U. S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: June 3, 2010

SUBJECT: **Tolfenpyrad:** Human Health Risk Assessment for the Proposed Use of the New Active Ingredient on Ornamental Plants in Greenhouses.

PC Code: 090111	DP No.: D354437
Decision No.: 394868	Registration No.: 71711-GN
Petition No.: N/A	Regulatory Action: Section 3 Registration
Risk Assessment Type: Single Chemical, No aggregate	Case No.: N/A
TXR No.: N/A	CAS No.: 129558-76-5
MRID No.: N/A	40 CFR N/A

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1.0 Executive Summary

Nichino America, INC, has submitted a request for a Section 3 registration for a proposed use of a new active ingredient insecticide. Tolfenpyrad shows broad insecticidal activity against target pests through the egg, larval, nymph, and adult stages. The proposed use is for the control of thrips, aphids and scales on ornamental plants grown in greenhouses. There are no food or residential uses currently proposed for tolfenpyrad; however, food uses are anticipated in the future. The proposed use pattern will not likely result in residues in drinking water.

The end-use product, *Tolfenpyrad 15EC Insecticide* is formulated as an emulsifiable concentrate (EC) and contains 15% of the active ingredient, tolfenpyrad. It is applied by backpack sprayer, high and low pressure handwand. The total maximum single application rate (AR) is 0.003 lb ai/gallon of water. The application rates on crops with a consecutive application schedule range from 0.003 – 0.006 lb ai per gallon, per crop cycle, or growing season. In addition, 2 separate spray volumes are specified on the label, resulting in a range of application rates of 0.68 to 1.36 lb ai/A. Based on the number of seasonal applications (2 applications per crop cycle, with a minimum 10-day re-treatment interval) indicated on product labels and information provided by the registrant, non-dietary exposures are expected to be of short-, intermediate-, and long term durations for occupational handlers. Dermal short-, intermediate-, and long-term postapplication exposures are expected for workers conducting postapplication activities in greenhouses.

Hazard Characterization

A variety of toxic effects were noted in the toxicology database for tolfenpyrad. However, the most consistent finding across species and studies was effects on body weight and body weight gain. Decreases in body weight and/or body weight gain were observed in adults of all species (rat, mice, rabbit, and dog) in the majority of the subchronic oral and dermal toxicity studies, and all chronic toxicity studies. The rat is the species most sensitive to body weight changes, with effects observed at much lower doses than in other species. The body weight changes observed in other species were similar in magnitude to those in rats, but were observed at higher doses.

The body weight changes observed in the database were most often seen in the presence of decreased food consumption and in some studies, additional toxicity including liver/kidney effects and clinical signs. Moribundity and/or mortality were also noted in at least one study in all species. However, this was observed in the presence of body weight changes and mainly observed at the highest dose tested (HDT).

Based on the proposed nonfood use pattern for tolfenpyrad, FQPA considerations do not apply. However, since food uses are anticipated in the future, FQPA hazard considerations are discussed in detail in the hazard section. Based on the toxicology database, HED recommends that the 10X FQPA safety factor for the protection of infants and children, be reduced to 1X.

Tolfenpyrad is classified as “not likely to be carcinogenic to humans.”

For purpose of the current risk assessment, endpoints were selected for occupational short- and intermediate- inhalation exposure and short-, intermediate-, and long-term dermal exposures. For

dermal exposures, a route-specific 21-day dermal toxicity study in rats was used for endpoint selection. However, an extra 3x uncertainty factor (subchronic to chronic) was applied to long-term dermal risk assessments since a short-term dermal study was used to assess long-term dermal exposure.

For short-and intermediate-term inhalation exposures, a 4-week inhalation study was used for endpoint selection. No toxic effects were observed up to the NOAEL of 10 mg/m^3 (EPA calculated dose = 2.6 mg/kg/day) and the LOAEL was not determined. However, the applicant noted that mortality was observed in a range-finding study at 26 mg/m^3 (6.8 mg/kg/day). HED used the NOAEL of 2.6 mg/kg/day from the 4-week inhalation study for risk assessment; however, the range-finding study should be submitted to the Agency for review as a condition of registration.

For short-, and intermediate-term dermal and inhalation assessments, a combined uncertainty factor (UF) of 100 served as the basis for the level of concern (LOC) for occupational risk, or margins of exposure (MOEs). For the long-term dermal assessment, a combined uncertainty factor (UF) of 300 served as the basis for the level of concern (LOC). Therefore, for short-, and intermediate term dermal and inhalation risk assessments, MOEs greater than 100 are not of concern. For long-term dermal risk assessments, MOEs greater than 300 are not of concern.

Occupational Handlers Exposure

Data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 were used to assess handler exposures (HED Science Advisory Council for Exposure (ExpoSAC), SOP No. 7, January 1999). A summary of the risks for occupational handlers is included in Table 4. The maximum application rate for each exposure scenario was assessed (i.e., 0.003 lb ai/gal). All handler short- and intermediate-term scenarios resulted in MOEs greater than the level of concern (MOEs > 100) with risk mitigation (e.g., chemical-resistant gloves). Long-term handler risks were also not of concern (MOEs > 300). **HED recommends all handlers wear a long-sleeved shirt, long pants, socks, chemical-resistant gloves, and footwear as stated in the proposed label.**

Occupational Postapplication Exposure

Dermal

HED used default assumptions with respect to dissipation on ornamental plants, standard TCs for various postapplication activities, and "day 0" foliar residue values (i.e., residues after initial treatment). The two spray volumes specified on the label were used to determine the application rate on a per acre basis, in order to determine the potential exposure from contacting treated foliage; these per acre application rates were 0.68-1.36 lb ai/A. Short-term exposure and risk calculations were considered representative/protective of intermediate-term exposure and risk. Long-term exposure and risk were also calculated.

The short- and intermediate-term postapplication risks for ornamental crops were not of concern. Long-term postapplication MOEs are not of concern for low-medium contact activities (i.e., pruning, tying, hand pinching, and nursery activities). For long-term postapplication high contact activities (i.e., cutting flowers), a REI of 4 days would be needed to reach the target MOE of 300 at the maximum spray volume/A (AR=1.36 lb ai/A). However, it should be noted that long-term (≥ 6 months-1 year)

dermal postapplication exposure was estimated assuming the same residue calculated on day of initial treatment. HED believes the residue available for exposure after 6 months or longer is likely to be lower than the residue value estimated on day of initial treatment. Considering the nature of the residues used for risk assessment, the MOE = 210 (on day 0) for high contact postapplication activities (AR=1.36 lb ai/A) is recognized as a conservative risk estimate. Submission of a chemical-specific DFR study for greenhouses is recommended to refine the residue values and reduce this uncertainty for high contact scenarios.

Inhalation

The Worker Protection Standard (WPS) for Agricultural Pesticides contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements. Tolfenpyrad has a vapor pressure of 3.0×10^{-8} mm Hg. Although there is potential for postapplication inhalation exposure resulting from the use of tolfenpyrad in greenhouses, with proper use of ventilation, tolfenpyrad inhalation exposure is expected to be negligible. Therefore, a quantitative postapplication inhalation exposure assessment was not performed. This approach may be revisited in the future with potential changes in the Agency's approach for assessing inhalation exposure and risk.

Restricted Entry Interval

The REI specified on the proposed label is based on the acute toxicity of the tolfenpyrad technical material. Based on the acute toxicity profile of tolfenpyrad, the 24 hour REI appearing on the proposed label is appropriate for low, medium, and high contact postapplication activities.

Environmental Justice Considerations

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf.

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intakes by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups, and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, nondietary exposures based on home-use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently under evaluation as OPP has committed resources and expertise to the development of specialized software models and the refinement of current methodologies and policies that consider exposure to

bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups. To ensure that this risk assessment is consistent with scientific standards and policies under development, HED might refine the risk assessment components for all registered uses in the future.

Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED) and Agricultural Reentry Task Force (ARTF), have been determined to require a review of their ethical conduct, have received that review, and have been determined to be ethically conducted.

HED Conclusions/Recommendations

Risks for occupational handlers who apply Tolfenpyrad 15EC Insecticide on ornamental plants in greenhouses are not of concern to HED. Risks from short- and intermediate-term postapplication activities are also not of concern to HED. Risks from long-term postapplication activities have been assessed in a conservative manner and are detailed above.

Based on the current risk assessment, HED recommends:

- All handlers should wear a long-sleeved shirt, long pants, socks, chemical-resistant gloves and footwear as stated in the proposed label.
- The proposed label personal protective equipment (PPE) language should be revised to state the use of: "*Chemical-resistant gloves made of materials such as barrier laminate or polyvinyl chloride*."
- The default dislodgeable foliar residue (DFR) values and assumptions used in the assessment may be under or overestimated. Therefore, submission of a chemical-specific DFR study for greenhouses is recommended to reduce this uncertainty, and could potentially result in reduced exposure and risk estimates for all scenarios.
- To determine the exposure duration that needs to be assessed for future registration actions, the applicant could provide the Agency with information to characterize the use pattern for the end-use product (EP) containing tolfenpyrad. Such information might include specific seasonal information about the use to be assessed, major regions on which the product is applied and how the product fits with other active ingredients in pest resistance management programs.
- The Registration Division (RD) should ensure that the appropriate restricted reentry interval (REI) is included on the proposed label.
- Proprietary data from the Agricultural Reentry Task Force (ARTF) have been used in this assessment. The chemical review manager (CRM) is encouraged to pursue data compensation in the event the registrant is not a member of this respective task force.

Toxicology

- The requirement for the 90-day dermal toxicity study is not waived. As a condition of registration, HED recommends Nichino submit the dermal toxicity study with rats dosed up to the limit dose in an effort to better characterize long-term dermal exposure.
- As a condition of registration, the dose range-finding studies mentioned in the 4 week inhalation study (MRID 47447728) should be submitted to the Agency. It was stated that in a previously conducted study with groups of 3 rats/sex/concentration, mortality was observed after a single 6-hour exposure to 26 or 79 mg/m^3. In repeated dose studies, similar groups of rats tolerated a 4-day exposure at 11 mg/m^3 or 5 days at 3.6 mg/m^3

2.0 Ingredient Profile

Tolfenpyrad is a novel pyrazole insecticide proposed for use in the control of thrips, aphids and scales on ornamental plants grown in greenhouses. It has been registered in Japan, Dominican Republic, Thailand, and Taiwan. In addition to the United States, it is currently under development in Brazil. The chemical structure and nomenclature of tolfenpyrad are presented in Table 2.2, and the physicochemical properties of the technical grade of tolfenpyrad are presented in Table 2.3. The applicant has indicated that the active ingredient will be formulated as a 15% emulsifiable concentrate (EC) containing 1.25 lb ai/gal. The proposed use directions and application rates are summarized below in Table 2.1.

2.1 Summary of Proposed End Use Products/Use Patterns

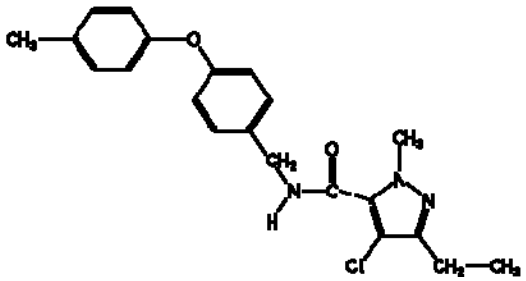
Table 2.1 summarizes the proposed use pattern and formulation specified in the end-use product containing tolfenpyrad. Applications of tolfenpyrad 15EC Insecticide are to be made using foliar spray equipment. The proposed label has personal protective equipment (PPE) recommendations which include: applicators and other handlers must wear long-sleeved shirt, long pants, socks, chemical-resistant gloves and footwear.

Table 2.1. Summary of Proposed Use Patterns and Formulations for Tolfenpyrad.

Formulation	Method of Application	Use Sites	Application Rate	Timing of Application
Tolfenpyrad 15EC Insecticide - emulsifiable concentrate (15% a.i.) **For Commercial use** EPA Reg #71711-XX (1.25 lb ai/gal)	foliar spray by low and high pressure handwand, backpack sprayer	greenhouse-grown ornamental plants (ash, yew, rose, evening primrose, gladiolus, cherry, arrowood, marigold, moss rose, new guinea impatiens, petunia, gerbera, chrysanthemum, coleus, poinsettia, schefflera, lantana)	Max single appl. rate = 0.00313 lb ai/gal (0.68 - 1.36 lb ai/A)‡	2 apps per crop cycle (0.006 lbs ai/gal); 24-hour REI; 10-day interval between apps; Apply uniformly. Do not apply more than 100 gallons per 20,000 ft^2 (218 gal/A) up to 10 gallons per 1,000 ft^2 (436 gal/A).

‡ Lower Spray Volume = 0.68 lb ai/A (at 100 gal/20,000 ft^2 = 218 gal/A)
0.00313 lb ai/gal * 218 gal/A = 0.68 lb ai/A
Higher Spray Volume = 1.36 lb ai/A (at 10 gal/1000 ft^2 = 436 gal/A)
0.00313 lb ai/gal * 436 gal/A = 1.36 lb ai/A

2.2 Structure and Nomenclature

Table 2.2. Test Compound Nomenclature.	
Chemical Structure	
Empirical Formula	$C_{21}H_{22}ClN_3O_2$
Common name	Tolfenpyrad, OMI, OMI-88, Hatchi-Hatchi
Company experimental name	N/A
IUPAC name	4-chloro-3-ethyl-1-methyl-*N*-[4-(*p*-tolyloxy)benzyl]pyrazole-5-carboxamide
CAS name	4-chloro-3-ethyl-1-methyl-*N*-[[4-(4-methylphenoxy)phenyl]methyl]-1*H*-pyrazole-5-carboxamide
CAS Registry Number	129558-76-5
End-use product/EP	*Tolfenpyrad 15EC Insecticide*
Chemical Class	pyrazole
Known Impurities of Concern	N/A

2.3 Physical and Chemical Properties

Table 2.2. Physicochemical Properties for Tolfenpyrad.		
Parameter	**Value**	**Reference**
Molecular Weight (TGAI)	383.9	MRID 47447704
Melting point/range (PAI)	85.5-88.5° C	MRID 47447705
pH (TGAI)	5.1	MRID 47447704
Density (TGAI)	1.25 g/cm^3	MRID 47447704
Water solubility (PAI)	0.061 mg/L	MRID 47447705
Solvent solubility (temperature not specified) (TGAI)	n-heptane 6.92 g/L Xylene 218 g/L 1,2 dichloroethane >250 g/L Methanol 50.8 g/L n-octanol 43.7 g/L Acetone 250 g/L Ethyl acetate 250 g/L	MRID 47447704
Vapor pressure (PAI)	4 x 10^{-5} Pa at 25 °C (= 3.0 x 10^{-8} mm Hg)	MRID 47447705

Table 2.2. Physicochemical Properties for Tolfenpyrad.		
Parameter	**Value**	**Reference**
Dissociation constant, pKa	No dissociation constant in the environmental pH range	MRID 47447705
Partition coefficient, $\log_{10}P_{OW}$ (PAI)	4.3	MRID 47447705

PAI= Purified Active Ingredient
TGAI-Technical Grade Active Ingredient

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

The toxicology database for tolfenpyrad is complete and the scientific quality of the submitted toxicity studies is relatively high. The toxicity profile can be characterized for potential systemic, carcinogenic, mutagenic, immunotoxic, developmental, and reproductive effects. Studies available for risk assessment included: acute oral, dermal, and inhalation toxicity, primary eye and dermal irritation and skin sensitization, subchronic oral toxicity (rat, mouse and dog), 21-day dermal toxicity and dermal penetration (rat), 4-week inhalation (rat), acute and subchronic neurotoxicity (rat), chronic dog, combined chronic/carcinogenicity (rat) and carcinogenicity (mouse), developmental toxicity (rat and rabbit), developmental immunotoxicity (rat), two-generation reproduction (rat), mutagenicity battery, and general metabolism. A developmental neurotoxicity (DNT) study was not included, but is not warranted at this time.

3.1.1.1 Mode of action, metabolism, toxicokinetic data

Tolfenpyrad is a pyrazole insecticide that impairs respiration of target pests through the inhibition of complex 1 of the mitochondrial respiratory electron transport chain. This results in very rapid insecticidal responses, including cessation of movement and feeding, lack of fecundity and eventual death of the pest.

3.1.2 Toxicological Effects

A variety of toxic effects were noted in the toxicology database for tolfenpyrad. However, the most consistent finding across species and studies was body weight and body weight gain. Decreases in body weight and/or body weight gain were observed in adults of all species (rat, mice, rabbit, and dog) in the majority of the subchronic oral and dermal toxicity studies, and all chronic toxicity studies.

The rat is the species most sensitive to body weight changes, with effects observed at much lower doses than in other species. In rats, significant decreases in body weight and body weight gain were observed in subchronic oral and acute and subchronic neurotoxicity studies. Decreases in body weight and body weight gain were also seen in chronic rat studies but at lower doses than observed in the other rat studies. However, although seen at lower doses, the body weight decrements noted in the chronic study were not as pronounced as seen after subchronic exposure or in the neurotoxicity studies. Decreases in body weight and body weight gain were also observed in reproduction, developmental

toxicity, and developmental immunotoxicity studies at doses comparable to the chronic study. Significant decreases in body weight gain and food consumption were also seen in a 21-day dermal toxicity study but in the absence of any other systemic toxicity.

Body weight changes observed in other species were similar in magnitude to those in rats, but were observed at higher doses. Significant decreases in body weight and body weight gain were seen in both mice and dogs after subchronic exposure; these effects were also noted in rabbits in a developmental toxicity study. Chronic exposure resulted in body weight and body weight gain decreases in mice and dogs at lower doses. The severity of body weight changes increased with dose in mice while body weight effects in dogs were seen only at the highest dose tested (HDT).

The body weight changes observed in the database were most often seen in the presence of decreased food consumption and in some studies, additional toxicity including liver/kidney effects and clinical signs. Increased liver and kidney weights, liver and kidney hypertrophy, hyaline droplets in the kidney, and color change in the kidney were seen after subchronic exposure in rats. Chronic exposure resulted in similar effects along with color changes in the liver and liver histopathology at slightly lower doses than in the subchronic studies. Other effects noted in rats were effects on the harderian gland and lymph nodes. In dogs, both liver and kidney histopathology, along with testicular atrophy and clinical signs (emaciation, decreased movement, and staggering gait) were seen in short-term studies. Long-term exposure resulted in histopathology in the liver only, along with increased liver enzymes. No treatment-related effects were noted in the liver or kidney in mice. However, rough coats, hunched posture, ataxia, and hypoactivity were seen in subchronic studies. Missing ears and ear lesions (scabs, sores, ulceration, and inflammation) were seen in a chronic toxicity study. The ear lesions observed were likely self inflicted since the mice in the study were individually caged. No explanation was given to why the lesions occurred and the toxicological significance of this finding is unclear.

Moribundity and/or mortality were noted in at least one study in all species and mainly observed at the HDT. Moribundity and mortality were noted in two dams in a rat reproduction study, and mortality was noted in one dam in a rabbit developmental toxicity study. In mice and dogs, mortality was observed in both subchronic and chronic toxicity studies. In all cases, effects were observed in the presence of body weight changes.

Several adverse effects were noted in young animals in developmental toxicity and reproduction studies; however, the effects were observed in the presence of significant maternal toxicity (significant body weight changes and/or moribundity/mortality). No evidence of increased quantitative or qualitative susceptibility was observed in the studies. In a developmental immunotoxicity study in rats, a potential increase in qualitative susceptibility was seen. In the study, decreased survival, body weight, body weight gain, increased blackish abdominal cavity, and dark green abnormal intestinal contents were observed in offspring animals at 3 mg/kg/day. At the same dose, decreased body weight (up to 10%), body weight gain (up to 36%) and food consumption were seen in maternal animals. There was no evidence of immunotoxicity observed in the study.

No evidence of neurotoxicity was observed in acute and subchronic neurotoxicity studies for tolfenpyrad. Although hunched posture, ataxia, and hypoactivity were seen in mice in a 28 day toxicity study, these effects were not seen in a 90 day study or after chronic exposure. In dogs,

decreased spontaneous movement, and staggering gait were observed after 13 weeks. In rats, decreased motor activity and prone position (lying face down) prior to death were noted in a reproduction study. Overall, the effects noted in the database were agonal effects mainly seen at high doses, not associated with neuropathology, and not noted in long-term studies. The effects observed are consistent with the mode of action for tolfenpyrad (mitochondrial inhibitor) and are not considered evidence of neurotoxicity.

In a rat dermal toxicity study (21 days), decreased body weight gain and food consumption were observed in the absence of any other systemic toxicity. A rat dermal penetration study is also available which resulted in a dermal absorption factor (DAF) of 13%.

No evidence of carcinogenicity was observed in cancer studies with mice and rats. Therefore, in accordance with EPA's Final Guidelines for Carcinogen Risk Assessment (March, 2005), tolfenpyrad is classified as "not likely to be carcinogenic to humans."

3.1.3 Dose-response

Based on the proposed nonfood use pattern for tolfenpyrad, FQPA considerations do not apply. However, since food uses are anticipated in the future, endpoints were selected for dietary exposures. For acute dietary exposure, an acute reference dose (aRfD) of 0.1 mg/kg/day was selected for assessment of the general population, based on a NOAEL of 10 mg/kg/day in an acute neurotoxicity study in rats. At the LOAEL of 20 mg/kg/day, decreased body weight, body weight gain, and food consumption were seen. The effects were observed after a single dose exposure in a dietary study and are considered appropriate for acute dietary exposure. No separate endpoint was identified for acute dietary exposure for females 13-49 years of age.

For chronic dietary exposure, a chronic reference dose (cRfD) of 0.006 mg/kg/day was selected for assessment of all populations, based on a NOAEL of 0.6 mg/kg/day from a combined chronic/carcinogenicity study in rats. Decreased body weight, body weight gain and food consumption, changes in the harderian glands (found in the eye), histopathological changes in liver, kidney and lymph nodes were observed at the LOAEL of 1.5 mg/kg/day. Chronic mouse and dog studies were also considered for chronic dietary exposure; however, the chronic rat study provided the most sensitive endpoint for chronic dietary risk assessment.

For the purpose of the current risk assessment, endpoints were selected for occupational short- and intermediate-term inhalation exposure and short-, intermediate-, and long-term dermal exposure. For dermal exposures, a route-specific 21-day dermal toxicity study in rats was used for endpoint selection. However, an extra 3x uncertainty factor (subchronic to chronic) was applied to long-term dermal risk assessments since a short-term dermal study was used to assess long-term dermal exposure.

For short-and intermediate-term inhalation exposures, a 4-week inhalation study was used for endpoint selection. No toxic effects were observed up to the NOAEL of 10 mg/m^3 (EPA calculated dose = 2.6 mg/kg/day) and the LOAEL was not determined. However, the applicant noted that mortality was observed in a range-finding study at 26 mg/m^3 (6.8 mg/kg/day). HED used the NOAEL of 2.6 mg/kg/day from the 4-week inhalation study for risk assessment; however, the range-finding study should be submitted to the Agency for review.

3.1.4 FQPA

Based on the proposed nonfood use pattern for tolfenpyrad, FQPA considerations do not apply. However, since food uses are anticipated in the future, FQPA hazard considerations were addressed in HED's evaluation of the submitted data and are discussed in section 3.3.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

Several metabolism studies were conducted with radiolabeled tolfenpyrad in rats (MRIDs 47447837, 47447836, 47447834). Overall, absorption, excretion, and metabolism of the test compound was rapid. Following a single oral dose, radioactivity was detected in the blood 0.5 h after administration. Blood concentrations of radioactivity plateaued after the third administration in the multiple dose study, suggesting there was no bioaccumulation following repeated administration. The highest concentrations of radioactivity were observed in the liver, kidney, brown fat and heart, with a redistribution that also included white fat, bone marrow and skin over time. Radioactivity concentrations dropped substantially from 12 to 168 h post-dosing.

Tolfenpyrad was excreted in a rapid and dose-dependent manner following a single exposure. After a 1 mg/kg single dose, approximately 67% of the administered dose (AD) was eliminated during the first 24 h post-dosing, increasing to 85% AD at 48 h. In the 20 mg/kg single dose groups, excretion was somewhat slower, with up to 30% AD eliminated during the first 24 h post-dosing, increasing to up to 70% AD at 48 h. Feces were the predominant route of excretion, accounting for up to 93% AD; residues in urine, expired air, and cage wash were negligible. Administration of repeated daily doses had no effect on the route of excretion or the extent of recovery. Tolfenpyrad was metabolized by oxidation to form a number of hydroxylated metabolites (Pt-CA, OH-PT and OH-PT-CA), followed by conjugation (glucuronide, sulfate, asparagines or taurine). The primary metabolite, PT-CA was found in plasma, liver, kidney, and fat (<5%), along with taurine-conjugated and hydroxylated forms, in the bile at 4.6-22.3%. Higher levels of PT-CA were found in the feces (9.0-36.2% AD); however, it was stated in the study that the additional PT-CA is likely formed by the action of the enterobacteria in the gut. Parent was identified in the feces at only at 0.3-14.8% AD, and the amount decreased with time.

There were no significant differences observed in the blood pharmacokinetic parameters between the [PY-^{14}C]- and [TO-^{14}C]-label positions in the single or multiple dose studies. However, in animals given multiple doses of pyrazole-labled (^{14}C) tolfenpyrad, blood levels of radioactivity were approximately 2- to 3-fold higher in females than in males. Females also had more radioactivity remaining in the gastrointestinal tract, and the amount remaining increased with dose. Conversely, absorption (defined as radioactivity found in the bile, urine, cage wash, and carcass) was greater in males (72.8-77.8% AD) than in females (57.9-69.4% AD).

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

The toxicology database for tolfenpyrad is adequate to characterize potential pre- and/or post-natal toxicity for assessing risks for infants and children. Acceptable studies for developmental toxicity in rats and rabbits, developmental immunotoxicity, 2-generation reproduction in rats, and neurotoxicity are available for FQPA assessment.

3.3.2 Evidence of Neurotoxicity

The clinical signs observed in the toxicology database are consistent with the mode of action (mitochondrial inhibitor) for tolfenpyrad and not considered evidence of neurotoxicity. Hunched posture, ataxia, and hypoactivity were seen in mice after 28 days at 104/126 mg/kg/day. These effects were not seen in a 90 day study in mice up to 46.2/57.9 mg/kg/day or after chronic exposure in mice up to 20.8/27.1 mg/kg/day. In dogs, decreased spontaneous movement, and staggering gait were observed after 13 weeks at 30 mg/kg/day. In rats, decreased motor activity and prone position (lying face down) prior to death were noted in a reproduction study at 3.0 mg/kg/day. Overall, the effects noted in the database were agonal effects, mainly seen at high doses, not associated with neuropathology, and not noted in long-term studies. No neurotoxic effects were noted in acute or subchronic neurotoxicity studies in rats.

3.3.3 Developmental Toxicity and Reproduction Studies

In a developmental toxicity study in rats, decreased body weight gain and food consumption were seen at 3 mg/kg/day (LOAEL) in maternal animals, while no effects were seen in fetuses at this dose. At 4.5 mg/kg/day, decreases in body weight were seen in addition to decreases in body weight gain and food consumption. Additionally at 4.5 mg/kg/day (LOAEL), fetal effects included increased incidences of 14^{th} ribs, decreased fetal body weights, and decreased number of ossified metacarpals.

In a developmental toxicity study in rabbits, there were no maternal or developmental effects observed up to 6 mg/kg/day. However, a single mortality, emaciation, decreased body weights, body weight gains, and food consumption were seen in maternal animals in the developmental range-finding study at 9 mg/kg/day. Also at 9 mg/kg/day, early resorption and incidences of supernumerary coronary orifices, fusion of the ossification centers of the caudal vertebral bodies, 13^{th} ribs, and delayed ossification of the manus were seen in fetuses.

In a developmental immunotoxicity study in rats, decreased body weight, body weight gain and food consumption were observed in maternal animals at 3 mg/kg/day. In offspring, decreased survival, body weight, body weight gain, increased blackish abdominal cavity, and dark green abnormal intestinal contents were seen at 3 mg/kg/day.

In a 2-generation reproduction study in rats, decreased body weight and body weight gains, decreased motor activity, reddish tears, and prone position prior to death in two dams were seen in parental animals at 3.0 mg/kg/day. Additionally, decreased gestation index, increased gestation duration, abnormal parturition, and total litter loss were observed in female animals at 3.0 mg/kg/day. In pups,

decreased pup viability and body weights, as well as delays in attainment of developmental landmarks (eye opening, pinna folding, surface righting reflex) were observed at 3.0 mg/kg/day.

3.3.4 Additional Information from Literature Sources

A literature search did not reveal information that would impact the hazard or risk assessment.

3.3.5 Pre-and/or Postnatal Toxicity

3.3.5.1 Determination of Susceptibility

No evidence of increased quantitative or qualitative susceptibility was observed in developmental toxicity studies in rats or rabbits or a reproduction toxicity study in rats. However, a potential increase in qualitative susceptibility was seen in a developmental immunotoxicity study in rats. In the study, decreased survival, body weight, body weight gain, increased blackish abdominal cavity, and dark green abnormal intestinal contents were seen in offspring animals at 3 mg/kg/day. At the same dose, decreased body weight (up to 10%), body weight gain (up to 36%) and food consumption were observed in maternal animals.

3.3.5.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

The purposes of the Degree of Concern analyses are to determine the level of concern for the effects observed when considered in the context of all available toxicity data, and to identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment. If residual uncertainties are identified, then HED determines whether these residual uncertainties can be addressed by an FQPA safety factor and, if so, the size of the factor needed.

Although there is possibly increased qualitative susceptibility in the young in the developmental immunotoxicity study (DIT) in rats, there is low concern and there are no residual uncertainties regarding increased quantitative or qualitative pre- and/or postnatal susceptibility. In the DIT at 3 mg/kg/day, significant decreases in body weight and body weight gain were observed in the maternal animals while decreased survival was seen in the offspring. The severity in pup effects compared to maternal suggests qualitative susceptibility. However, in developmental and reproduction studies in rats of the same strain and at the same dose, maternal mortality was observed in concert with less severe effects in offspring animals. When the DIT is considered along with the developmental and reproduction studies, it is likely that 3 mg/kg/day results in moribundity/mortality in maternal animals. Therefore, HED does not consider the isolated incident in the DIT a true indicator of qualitative susceptibility. Additionally, there is no evidence of quantitative susceptibility (effects occurred in the presence of maternal toxicity) in the study, a clear NOAEL was identified for the offspring effects seen, and no evidence of increased quantitative or qualitative susceptibility was seen in the developmental (rat and rabbit) or reproduction studies. Furthermore, the risk assessments are based on the most sensitive endpoints, and the NOAELs selected are considered protective of potential developmental and offspring effects. Considering the overall toxicity profile and the doses and endpoints selected for risk assessment for tolfenpyrad, the degree of concern for the effects observed in the DIT study is low. Therefore, HED recommends the FQPA factor be reduced to 1X (see 3.4).

3.3.6 Recommendation for not requiring a Developmental Neurotoxicity Study

Clinical signs consistent with the mode of action (mitochondrial inhibitor) for tolfenpyrad were observed in the toxicology database (sec. 3.3.2.). The effects observed were mainly seen at high doses, not associated with neuropathology, and not noted in long-term studies. Additionally, no neurotoxic effects were observed in acute or subchronic neurotoxicity studies in rats and there are no residual concerns for increased quantitative or qualitative susceptibility. Therefore, based on the overall toxicity database and the weight of the evidence, a developmental neurotoxicity study is not warranted at this time.

3.4 FQPA Safety Factor for Infants and Children

As mentioned previously, the proposed nonfood use pattern for tolfenpyrad does not require FQPA considerations. However, food uses are anticipated in the future so FQPA hazard considerations were addressed in HED's evaluation. HED recommends that the 10X FQPA safety factor for the protection of infants and children, be reduced to 1X based on hazard considerations alone, since there are no potential food or residential exposures expected for the current actions. Once the food uses are submitted, HED will include the exposure assessment in the final conclusion regarding the FQPA safety factor. The decision to reduce the factor to 1X is based on the following hazard considerations:

- The toxicological database is complete for the purpose of FQPA assessment.
- There are no concerns for increased quantitative and qualitative susceptibility or residual uncertainties for pre-and postnatal toxicity. Although there is possibly increased qualitative susceptibility in the young in the developmental immunotoxicity study (DIT) in rats, there is low concern as discussed previously in Section 3.3.5.2
- There is no concern for neurotoxicity, and a developmental neurotoxicity study (DNT) is not required.

3.5 Hazard Identification and Toxicity Endpoint Selection

3.5.1 Acute Reference Dose (aRfD) – All Populations

Study Selected: Acute Neurotoxicity Study in Rats
MRID No: 47447831
Dose and Endpoint for Risk Assessment: NOAEL= 10 mg/kg/day, based on decreased body weight, body weight gain and food consumption observed at the LOAEL of 20 mg/kg/day.
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

$$\textbf{Acute RfD} = \frac{10\ mg\ /\ kg\ /\ day}{100\ (UF\ )} = \textbf{0.1 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factors:
Although body weight changes are not usually the result of a single dose exposure, significant decreases in body weight (6-12%) and decreases in bodyweight gain (26%) were observed after a single dose exposure in a dietary study and are appropriate for acute dietary exposure.

No separate endpoint was identified for acute dietary exposure for females 13-49 years of age. Resorptions seen in a range-finding developmental toxicity study in rabbits were considered for endpoint selection. However, the resorptions were seen in the presence of significant maternal effects (emaciation, body weight changes, and mortality) and are considered secondary to maternal toxicity and not a result of a single exposure. Therefore, the endpoint is not applicable to acute dietary risk assessment.

3.5.2 Chronic Reference Dose (cRfD)

Study Selected: Combined Chronic Toxicity/Carcinogenicity Study in Rats
MRID No: 47463704
Dose and Endpoint for Risk Assessment: NOAEL= 0.6 mg/kg/day, based on decreased body weight, body weight gain and food consumption of females, changes in the harderian glands (found in the eye) of males, histopathological changes in liver, kidney and lymph nodes in females, and histopathological changes in the kidney of males, observed at the LOAEL of 1.5 mg/kg/day.
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

$$\textbf{Chronic RfD} = \frac{0.6\,mg\ /\ kg\ /\ day}{100\ \ (UF\ )} = \textbf{0.006mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factors:
The study is appropriate for chronic dietary exposure due to the route (oral) and long-term duration of dosing. In addition, the dose selected is the lowest NOAEL in the toxicity database, and will therefore be protective of other observed toxic effects. Chronic mouse and dog studies were also considered for chronic dietary exposure; however, the chronic rat study provided the most sensitive endpoint for chronic dietary risk assessment.

3.5.3 Dermal Absorption

A dermal penetration study in rats is available for tolfenpyrad. In the study, tolfenpyrad was applied to the shaved skin of Sprague Dawley rats. Four males/dose/time points were tested with termination times of 0.5, 1, 2, 4, 10, or 24 hours post-administration. Analytical recoveries were 89-96 % AD. Very little of the applied dose was actually absorbed at any concentration, ranging from approximately 6-13% absorbed at 24 hours post-dosing. Absorption continued throughout the 24 hour post-dosing period.

Based on HED policy, the most appropriate dermal absorption value for risk assessment is based on the results from the mid-dose group (1 g/L; actual dose 8.4 µg/cm^2 skin), as percent dermal absorption was greatest at this dose level. Since absorption continued throughout a 24 hour post-dosing period, the dermal absorption factor (DAF) of 13% was selected based on measurements at this time point.

However, a DAF was not used in the current risk assessment since the dermal point of departures are based on a route-specific study (21-day dermal toxicity).

3.5.5 Occupational Dermal Exposure

Short- and Intermediate-Term Dermal Exposure (up to 6 months of exposure)

Study Selected: 21-day dermal toxicity in rats
MRID No: 47447806
Dose and Endpoint for Risk Assessment: NOAEL= 200 mg/kg/day
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

Comments about Study/Endpoint/Uncertainty Factors:
Although decreased body weight gain and food consumption were noted at ≥ 50 mg/kg/day, these effects were not considered adverse and thus the highest dose tested (HDT) of 200 mg/kg/day was considered to be a NOAEL. There was no dose response relationship between tolfenpyrad exposure and decreased body weight gain and food consumption in the study, since decreases were similar at both 50 and 200 mg/kg/day. HED believes the lack of a dose response may be the result of saturation at doses ≥ 50 mg/kg/day. Since the dermal toxicity study did not test up to limit dose (1000 mg/kg/day), the 200 mg/kg/day was used as the NOAEL for dermal risk assessments. The study is route-specific and the duration is appropriate for short-, and intermediate-term dermal exposure.

The developmental toxicity studies (rats and rabbits), the developmental immunotoxicity study in rats and the reproduction study in rats were all considered for short-and intermediate-term dermal risk assessment. However, since there is no evidence of increased quantitative susceptibility between the young and the adult (i.e., developmental/offspring toxicity occurred at the same dose level as adult toxicity) the Agency concluded that selecting points of departure from route-specific studies that are protective for adults would also be protective for developmental/offspring effects. As a result, the dermal toxicity study is protective of potential offspring effects since it adequately measured systemic toxicity in maternal animals.

Long-Term Dermal Exposure (> 6 months of exposure)

Study Selected: 21-day dermal toxicity in rats
MRID No: 47447806
Dose and Endpoint for Risk Assessment: NOAEL= 200 mg/kg/day
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)
Uncertainty Factor: 300x (10x interspecies extrapolation, 10x intraspecies variability, 3x subchronic to chronic)

Comments about Study/Endpoint/Uncertainty Factors:
The available subchronic (21-day) route specific dermal study is not of an appropriate duration for long-term exposure. Therefore, although the 21-day dermal study was used for long-term dermal risk assessment, an extra uncertainty factor of 3x was applied for subchronic to chronic extrapolation. The 3x uncertainty factor is a data derived factor obtained by comparing the LOAELs from the available

rat subchronic toxicity studies and chronic toxicity studies. In the 90 day, developmental, and reproduction toxicity studies the LOAELs range from approximately 3 to 5 mg/kg/day; the LOAEL in the chronic toxicity study is approximately 2 mg/kg/day. Since there is a 2-3x difference between the subchronic and chronic toxicity studies, the extra UF of 3x is considered protective of potential effects when extrapolating from subchronic to chronic exposure.

The combined chronic/ carcinogenicity study was also considered for risk assessment. However, the route-specific study was considered more appropriate and the extra factor applied is considered protective of potential long-term effects.

3.5.6 Occupational Inhalation Exposure

Short- and Intermediate-Term Inhalation Exposure (up to 6 months of exposure)

Study Selected: 4 week inhalation toxicity study in rats
MRID No: 47447728
Dose and Endpoint for Risk Assessment: NOAEL= 10 mg/m^3 (2.6 mg/kg/day). No treatment-related effects were observed in the 4 week inhalation study. Mortality was observed in a range-finding study at 26 mg/m^3 (6.8 mg/kg/day day).

Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

Comments about Study/Endpoint/Uncertainty Factors:
No toxic effects were observed up to 10 mg/m^3 (EPA calculated dose = 2.6 mg/kg/day) in the main study; however, mortality was observed in a range-finding study at 26 mg/m^3 (6.8 mg/kg/day), as stated in the inhalation study report. However, the detailed results of the range-finding study were not included, and should be submitted for review as a condition of registration. The developmental toxicity studies (rats and rabbits), the developmental immunotoxicity study in rats and the reproduction study in rats were all considered for short-and intermediate-term inhalation risk assessment. However, the inhalation study was selected because it is a route specific study and considered more appropriate for inhalation risk assessment than the oral studies. There is no evidence of increased quantitative susceptibility between the young and the adult (i.e., developmental/offspring toxicity occurred at the same dose level as adult toxicity) and the Agency concluded that selecting points of departure from route-specific studies that are protective for adults would also be protective for developmental/offspring effects. Therefore, the inhalation study it is protective of potential offspring effects since it adequately measured systemic toxicity in adult animals.

3.5.7 Level of Concern for Margin of Exposure

The level of concern (LOC) for short-, and intermediate-term occupational dermal and inhalation risk assessment is 100. This includes conventional uncertainty factors of 10x for interspecies extrapolation and 10x for intraspecies variability. The LOC for long-term occupational dermal risk assessment is 300. This includes the conventional uncertainty factors and an extra 3x uncertainty factor (subchronic to chronic) for the use of a short-term study to assess long-term exposure. The FQPA factor has been reduced to 1x and no other factors are warranted.

Table 3.5.7 Summary of Levels of Concern for Risk Assessment.			
Route	Short-Term (1 - 30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	300
Inhalation	100	100	N/A

3.5.8 Recommendation for Combining Routes of Exposure for Risk Assessments

When there are potential occupational and residential exposures to a pesticide, the risk assessment must address exposures from three major sources: oral, dermal and inhalation exposures and determine whether the individual exposures can be combined if they have the same toxicological effects. For purposes of this risk assessment, there are no routes of exposure to combine.

3.5.9 Classification of Carcinogenic Potential

There was no evidence of carcinogenicity in cancer studies with mice and rats. Therefore, in accordance with EPA's Final Guidelines for Carcinogen Risk Assessment (March, 2005), tolfenpyrad is classified as "not likely to be carcinogenic to humans."

3.5.10 Summary of Toxicological Doses and Endpoints for Use in Human Risk Assessments

3.5.10a **Note:** There are currently no food or residential uses associated with Tolfenpyrad; however, endpoints have been chosen in anticipation of any future food or residential uses.

Table 3.5.10a Summary of Toxicological Doses and Endpoints for Tolfenpyrad for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	NOAEL= 10 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF=1x	Acute RfD = 0.1 mg/kg/day aPAD = 0.1 mg/kg/day	LOAEL=20 mg/kg/day from an acute neurotoxicity study in rats, based on decreased body weight body weight gain and food consumption.
Chronic Dietary (All Populations)	NOAEL= 0.6 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF=1x	Chronic RfD = 0.006 mg/kg/day cPAD = 0.006 mg/kg/day	LOAEL = 1.5 mg/kg/day from a combined chronic/carcinogenicity in rats, based on decreased body weight, body weight gain, and food consumption of females, gross changes in the Harderian glands of males, and histopathological changes in the liver, kidney and mesenteric lymph nodes of females and the kidney of males.

Table 3.5.10a Summary of Toxicological Doses and Endpoints for Tolfenpyrad for Use in Dietary and Non-Occupational Human Health Risk Assessments.				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-Term And Intermediate-Term (Up to 6 months of exposure)	NOAEL= 200 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF=1x	Residential LOC for MOE = 100	No LOAEL determined in 21-day dermal study in rats; not tested up to the limit dose of 1000 mg/kg/day. Only minimal changes in body weight gain (no absolute body weight changes) and food consumption were observed in the study and not considered adverse.
Dermal Long-Term (>6 months)	NOAEL= 200 mg/kg/day	UF_A= 10 x UF_H=10 x UF_S=3 x FQPA SF=1x	Residential LOC for MOE = 300	No LOAEL determined in 21-day dermal study in rats; not tested up to the limit dose of 1000 mg/kg/day. Only minimal changes in body weight gain (no absolute body weight changes) and food consumption were observed in the study and not considered adverse.
Inhalation Short-Term And Intermediate-Term (Up to 6 months of Exposure)	NOAEL= 2.6 mg/kg/day IAF = 100%	UF_A= 10 x UF_H=10 x FQPA SF=1x	Residential LOC for MOE = 100	No LOAEL determined 4 week inhalation study in rats. No effects observed up to 2.6 mg/kg/day in main study. Mortality observed at 6.8 mg/kg/day in a range-finding study.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_S = use of a short-term study for long-term risk assessment. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable. DAF = dermal absorption factor. IAF = inhalation absorption factor.

3.5.10b The following endpoints were chosen for the current risk assessment and apply to the proposed nonfood use on ornamentals.

Table 3.5.10b Summary of Toxicological Doses and Endpoints for Tolfenpyrad for Use in Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term And Intermediate-Term (Up to 6 months of Exposure)	NOAEL= 200 mg/kg/day	UF_A= 10 x UF_H=10 x	Occupational LOC for MOE = 100	No LOAEL determined in 21-day dermal study in rats; not tested up to the limit dose of 1000 mg/kg/day. Only minimal changes in body weight gain (no body weight changes) and food consumption were observed in the study and not considered adverse.
Dermal Long-Term (>6 months)	NOAEL= 200 mg/kg/day	UF_A= 10 x UF_H=10 x UF_S=3 x	Occupational LOC for MOE = 300	No LOAEL determined in 21-day dermal study in rats; not tested up to the limit dose of 1000 mg/kg/day. Only minimal changes in body weight gain (no body weight changes) and food consumption were observed in the study and not considered adverse.
Inhalation Short-Term And Intermediate-Term (Up to 6 months of Exposure)	NOAEL= 2.6 mg/kg/day IAF = 100%	UF_A= 10 x UF_H=10 x	Occupational LOC for MOE = 100	No LOAEL determined 4 week inhalation study in rats. No effects observed up to 2.6 mg/kg/day in main study. Mortality observed at 6.8 mg/kg/day in a range-finding study.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_S = use of a short-term study for long-term risk assessment. MOE = margin of exposure. LOC = level of concern.

3.6 Endocrine disruption

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed

to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

Tolfenpyrad is not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Under FFDCA sec. 408(p) the Agency must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP test orders/data call-ins for all pesticide active ingredients.

For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

4.0 Public Health Data

No public health/epidemiology data were used in developing this risk assessment.

5.0 Exposure Characterization/Assessment

Since this request is for a non-food use (greenhouse ornamentals), dietary, residential and drinking water exposure are not anticipated; therefore, assessments are not required for purposes of this risk assessment.

6.0 Aggregate Risk Assessment and Risk Characterization

Aggregate risk assessments are not needed at this time.

7.0 Cumulative Risk Characterization Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to tolfenpyrad and any other substances and tolfenpyrad does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that tolfenpyrad has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

8.0 Occupational Exposure and Risk

8.1 Handlers

Tolfenpyrad 15EC Insecticide is formulated as an emulsifiable concentrate (EC) and contains 15% of the ai, tolfenpyrad. The product is to be applied by backpack sprayer, high pressure handwand, and low pressure handwand equipment. The proposed maximum single application rate is 0.003 lb ai per gallon. The application rates range from 0.003 – 0.006 lb ai per gallon per crop cycle. In addition, two separate spray volumes are specified on the label, resulting in a range of application rates of 0.68 to 1.36 lb ai/A. Based on the number of seasonal applications (2 applications per crop cycle, with a minimum 10-day RTI) indicated on product labels and information provided by the registrant, non-dietary exposures are expected to be of short-, intermediate- and long-term durations for occupational handlers.

However, based on integrated pest management practices and chemical rotations, long-term handler exposures are considered to be less likely and any assessments of such exposures are likely to be conservative. No handler activities are expected for more than 6 consecutive months. Since doses selected for short-, intermediate- and long-term assessments are the same, the short-term exposure and risk assessment is protective of long-term exposures.

The following handler exposures result from dermal and inhalation routes for the proposed greenhouse uses:

- Mixing/Loading/Applying Liquid Formulation for High Pressure Handwand
- Mixing/Loading/Applying Liquid Formulation for Low Pressure Handwand
- Mixing/Loading/Applying Liquid Formulation for Backpack Sprayer

8.1.1. Data and Assumptions for Handler Exposure Scenarios

The assumptions, parameters and factors used for the exposure calculations include:

- Application rates were based on the proposed label. Maximum application rate on proposed label = 32 oz/100 gal. Product contains 1.25 lb ai/gal (0.0098 lb ai/fl oz).
  Maximum Single Application Rate = 32 oz/100 gal * 0.0098 lb ai/fl oz = 0.00313 lb ai/gal

- Unit Exposures: Chemical-specific data for assessing exposure during pesticide handling activities were not submitted to the Agency in support of this Section 3 application. It is HED policy to use data from PHED to assess handler exposures for regulatory actions when chemical-specific data are not available (HED ExpoSAC, SOP No. 7, January 1999).

  The baseline clothing level was used as a starting point to calculate handler exposures, even though the proposed label recommends the use of baseline clothing plus chemical-resistant gloves. Depending upon the need for additional dermal protection, additional PPE is added to obtain an MOE higher than the LOC. The baseline clothing level for occupational exposure scenarios generally represents an individual wearing long pants, a long-sleeved shirt, shoes, socks, no chemical-resistant gloves, and no respirator. As reflected in the calculations included herein, PPE may involve the addition of chemical-resistant gloves. For handlers mixing/loading and applying liquids with high and low pressure handwand and backpack sprayer, no data are available to assess

risks at baseline attire. Therefore, those handler scenarios were assessed at baseline plus chemical-resistant gloves.

The proposed label has PPE recommendations which include:

- Applicators and other handlers must wear a long-sleeved shirt, long pants, socks, chemical-resistant gloves and footwear.

- Area Treated: Based on HED's Exposure Science Advisory Committee SOP Number 9.1, the following gallons per day were assumed:

    - 40 gallons/day for mixing/loading/applying liquids using low-pressure handwand, and backpack sprayer.

    - 1000 gallons/day for mixing/loading/applying liquids using high pressure handwand.

- Body Weight: The average adult body weight of 70 kg was used for all calculations, since the endpoints selected for risk assessment were not sex-specific.

8.1.2. Exposure and Risk

Summaries of the short-term risks (MOEs) at baseline (a long-sleeved shirt, long pants, shoes, and socks), and at baseline plus chemical-resistant gloves for handlers, are included in Table 8.1.2. The results indicate that dermal and inhalation risks do not exceed HED's LOC, with MOEs greater than 100 at the baseline clothing scenario with the addition of chemical-resistant gloves, which are already specified on the proposed label.

HED recommends that the proposed label PPE language be amended from:

"Chemical-resistant gloves made of any waterproof material such as barrier laminate or polyvinyl chloride" to "Chemical-resistant gloves made of materials such as barrier laminate or polyvinyl chloride."

Table 8.1.2. Short- and Intermediate-Term Handler Exposure for Tolfenpyrad.										
Exposure Scenario	**Mitigation Level[a]**	**Dermal Unit Exposure[b] (mg/lb ai)**	**Inhalation Unit Exposure [b] (mg/lb ai)**	**Crop**	**Application Rate[c]**	**Amount Treated[d]**	**Dermal Dose[e] (mg/kg/day)**	**Dermal MOE[f]**	**Inhalation Dose[g] (mg/kg/day)**	**Inhalation MOE[h]**
Short- and Intermediate-Term										
Mixing/Loading and Applying liquids for high pressure handwand application (PHED data)	Single layer, Gloves	2.5	0.120 mg/lb ai	Ornamentals	0.00313 lb ai/gal	1,000 gallons/day	0.11179	1,800	0.00537	480
Mixing/Loading and Applying liquids for low pressure handwand (PHED data)	Single layer, Gloves	0.43	0.03 mg/lb ai	Ornamentals	0.00313 lb ai/gal	40 gallons/day	0.00077	260,000	0.00005	48,000
Mixing/Loading and Applying liquids for backpack sprayer application (PHED data)	Single layer, Gloves	2.50	0.03 mg/lb ai	Ornamentals	0.00313 lb ai/gal	40 gallons/day	0.00447	45,000	0.00005	48,000

a. Baseline Dermal: Long-sleeve shirt, long pants, and no gloves. Baseline plus Gloves Dermal: Baseline plus chemical-resistant gloves.
b. Unit Exposures based on PHED Version 1.1.
c. Application Rates based on proposed use on label for tolfenpyrad.
d. Exposure Science Advisory Council Policy No. 9.1.
e. Dermal Dose (mg/kg/day) = Daily Unit Exposure (mg/lb ai) x Application Rate (lb ai/gal) x Gallons Treated / Body Weight (70 kg).
f. Dermal MOE = NOAEL (200 mg/kg/day) / Dermal Daily Dose (mg/kg/day). Short- and Intermediate-Term LOC = 100; Long-term LOC = 300
g. Inhalation Dose (mg/kg/day) = Daily Unit Exposure (µg/lb ai) x Application Rate (lb ai/acre) x Acres Treated / Body Weight (70 kg).
h. Inhalation MOE = NOAEL (2.6 mg/kg/day) / Inhalation Daily Dose (mg/kg/day). Level of concern = 100.

8.2 Postapplication

Based on the number of seasonal applications indicated on these product labels, the proposed greenhouse use pattern, and information provided by the registrant, postapplication exposures are expected to be short- (1-30 days), intermediate- (1-6 months), and long-term (≥ 6 months-1 year) in duration. However, only short-term and long-term exposures were quantitatively assessed. Since doses selected for short- and intermediate-term assessments are the same, the short-term exposure and risk assessment is protective of intermediate-term exposures. Since tolfenpyrad is going to be used on multiple rotational ornamental crops, workers are expected to conduct nursery postapplication activities and will potentially be exposed to foliar residues more than 6 consecutive months per year.

Since no chemical-specific data such as DFR studies were submitted to estimate postapplication exposure, postapplication activities were assessed using dermal TCs from ExpoSAC: ARTF Ornamental Plants Transfer Coefficients, April 2002, summarized in Table 8.2. In addition, default assumptions with respect to the fraction available for transfer and residue dissipation (as described below) were used, along with the following:

- Application Rate = 0.68 – 1.36 lb ai/A, representing the lower and higher spray volumes specified on the label and shown in Table 2.1.

- Exposure Duration = 8 hours per day

- Body Weight = 70 kg

The fraction of ai retained on foliage surfaces is assumed to be 20% (0.2) of the application rate on the day of initial treatment. This fraction is assumed to further dissipate at the rate of 10% (0.1) per day. These are standard values established by HED ExpoSAC when no information is known about possible bonding to soil and foliar surfaces and dissipation of the active ingredient over time.

HED generally assesses exposure at "day 0" (i.e., on the day of treatment), and if MOEs are below the LOC, HED determines how many days would be needed in order to achieve an MOE >100. These calculations take into consideration the type of reentry activities likely to occur for a given scenario. Higher contact activities (such as hand harvesting or harvesting cut flowers) result in higher exposures, and may require longer reentry intervals to be specified on the label.

Table 8.2 Anticipated Postapplication Activities and Dermal Transfer Coefficients for Greenhouse use of Tolfenpyrad.

Proposed Crops	Policy Crop/Group Category	Transfer Coefficients (cm^2/hr)	Activity	Reference†
Ornamentals	ash, yew, rose, evening primrose, gladiolus, cherry, arrowood,	110	outdoor ornamental pruning, tying	MRID 454695-01; ARTF Study No. ART043

	marigold, moss rose, new guinea impatiens, petunia, gerbera, chrysanthemum, coleus, poinsettia, schefflera, lantana	175	greenhouse hand pinching ornamentals; nurseries activities	MRID 453445-01; ARTF Study No. ART039
		400	harvest (workers moved plants to trucks and reorganized the gallon pots or containers)	MRID 454695-02; ARTF Study No. ART044
	Cut flowers	5100 (short-term)	hand-harvesting	MRID 465139-01
		2700 (intermediate- and long term)		

† The information in the table is based on proprietary and non-proprietary data.

8.2.1. Exposure and Risk

Inhalation

The WPS for Agricultural Pesticides contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements. Tolfenpyrad has a vapor pressure of 3.0×10^{-8} mm Hg. Although there is potential for postapplication inhalation exposure resulting from the use of tolfenpyrad in greenhouses, with proper use of ventilation, tolfenpyrad inhalation exposure is expected to be negligible. Therefore, a quantitative postapplication inhalation exposure assessment was not performed. This approach may be revisited in the future with potential changes in the Agency's approach for assessing inhalation exposure and risk.

Dermal

A summary of the postapplication MOEs and respective reentry intervals is provided in Table 8.2.1. Based on the number of seasonal applications indicated on the proposed product labels, and information provided by the registrant, postapplication exposures are expected to be short-intermediate- and long-term in duration for all ornamentals plants. Standard assumptions with respect to body weight, area treated, and TCs were used to calculate the MOEs for occupational reentry. Since the same endpoint was selected for short- and intermediate-term exposure, short-term exposure and risk are representative/protective of intermediate-term exposures. For long-term exposures, HED provided a comparison of the estimated number of days required before an MOE reached the LOC.

Two spray volumes were assessed with application rates ranging from 0.68-1.36 lb ai/A; the default approach was used for estimating REIs, since no DFR data were submitted.

The short- and intermediate-term postapplication assessments for ornamental crops resulted in MOEs of 100 or greater on "day 0" (immediately after application) for low, medium and high contact exposure activities (i.e., pruning, tying, hand pinching, nursery activities, and cutting flowers) and were not of concern.

Long-term postapplication MOEs are not of concern for low-medium contact activities (i.e.,

pruning, tying, hand pinching, and nursery activities). For long-term postapplication high contact activities (i.e., cutting flowers), a REI of 4 days would be needed to reach the target MOE of 300 at the maximum spray volume/A (AR=1.36 lb ai/A). However, it should be noted that long-term (≥ 6 months-1 year) dermal postapplication exposure was estimated assuming the same residue calculated on day of initial treatment (i.e., day "0" residue value). HED believes the residue available for exposure after 6 months or longer is likely to be lower than the residue value estimated on the day of initial treatment. The day "0" residue value used for long-term postapplication dermal assessment represents a high-end assumption. Considering the nature of the residues used for the long-term postapplication risk assessment, the MOE = 210 (on day 0) for high contact activities at the maximum spray volume/A (1.36 lb ai/A) is recognized as a conservative risk estimate.

Submission of a chemical-specific DFR study for greenhouses is recommended to refine the residue values and reduce the uncertainty for high contact scenarios.

Table 8.2.1. Short-, Intermediate- and Long-Term Postapplication Exposure and Risk for Tolfenpyrad.

Crops	Activity	Application Rate (lb ai/A)	DAT[a] (TC - cm^2/hr)	DFR[b] (ug/cm^2)	Daily Dose[c] (mg/kg/day)	MOE[d]
Short- and Intermediate-term						
Ornamentals	pruning, tying	0.68	0 (110 cm^2/hr)	1.523	0.0191	10,000
		1.36	0 (110 cm^2/hr)	3.046	0.0383	5,200
	hand pinching, nursery activities	0.68	0 (175 cm^2/hr)	1.523	0.0305	6600
		1.36	0 (175 cm^2/hr)	3.046	0.0609	3,300
	harvesting (workers moved plants to trucks and reorganized the gallon pots or containers)	0.68	0 (400 cm^2/hr)	1.523	0.0696	2,900
		1.36	0 (400 cm^2/hr)	3.046	0.1393	1,400
	hand harvesting; cutting flowers	0.68	0 (5100 cm^2/hr)	1.523	0.8878	230
		1.36	0 (5100 cm^2/hr)	3.046	1.7756	110

Table 8.2.1. Short-, Intermediate- and Long-Term Postapplication Exposure and Risk for Tolfenpyrad.						
Crops	**Activity**	**Application Rate (lb ai/A)**	**DAT[a] (TC - cm^2/hr)**	**DFR[b] (ug/cm^2)**	**Daily Dose[c] (mg/kg/day)**	**MOE[d]**
Short- and Intermediate-term						
Long-Term						
Ornamentals	pruning, tying	0.68	0 (110 cm^2/hr)	1.523	0.0191	10,000
		1.36	0 (110 cm^2/hr)	3.046	0.0383	5,200
	hand pinching, nurseries activities	0.68	0 (175 cm^2/hr)	1.523	0.0305	6,600
		1.36	0 (175 cm^2/hr)	3.046	0.0609	3,300
	harvesting (workers moved plants to trucks and reorganized the gallon pots or containers)	0.68	0 (400 cm^2/hr)	1.523	0.0696	2,900
		1.36	0 (400 cm^2/hr)	3.046	0.1393	1,400
	hand-harvesting	0.68	0 (2700 cm^2/hr)	1.523	0.4700	430
		1.36	0 (2700 cm^2/hr)	3.046	0.9400	**210**
			4 (2700 cm^2/hr)	1.999	0.6168	**320**

Note:
a. DAT = Days After Treatment. TC = Transfer Coefficient.
b. Dislodgeable Foliar Residue (DFR) = Application Rate (lb ai/A) x (1- Daily Dissipation Rate)^t x 4.54E8 ug/lb x 2.47E-8 A/cm^2 x 0.2
c. Short- and Intermediate-term Daily Dose = [DFR (ug/cm^2) x TC (cm^2/hr) x 0.001 mg/ug x 8 hrs/day] ÷ Body Weight (70 kg); Long-term Daily Dose = [DFR (ug/cm^2) x TC (cm^2/hr) x 0.001 mg/ug x 8 hrs/day] ÷ Body Weight (70 kg)
d. Short- and Intermediate-term MOE = NOAEL/Daily Dose (NOAEL = 200 mg/kg/day; LOC = 100).
e. Long-term MOE = NOAEL/Daily Dose (NOAEL = 200 mg/kg/day; LOC = 300).

8.3 Restricted Entry Interval

The REI specified on the proposed label is based on the acute toxicity of tolfenpyrad technical

material which is classified as Category III for acute dermal and inhalation toxicity, Category IV for dermal and eye irritation, and Category II for acute oral toxicity. Based on the acute toxicity profile of tolfenpyrad, the 24 hour REI appearing on the proposed label is appropriate for low, medium, and high contact postapplication activities.

9.0 Data Needs and Label Recommendations

9.1 Occupational Exposure

Based on the current risk assessment:

- All handlers should wear a long-sleeved shirt, long pants, socks, chemical-resistant gloves and footwear as stated in the proposed label.
- The proposed label personal protective equipment (PPE) language should be revised to state the use of: "*Chemical-resistant gloves made of materials such as barrier laminate or polyvinyl chloride.*"
- The default dislodgeable foliar residue (DFR) values and assumptions used in the assessment may be under or overestimated. Therefore, submission of a chemical-specific DFR study for greenhouses is recommended to reduce this uncertainty, and could potentially result in reduced exposure and risk estimates for all scenarios.
- To determine the exposure duration that needs to be assessed for future registration actions, the applicant could provide the Agency with information to characterize the use pattern for the end-use product (EP) containing tolfenpyrad. Such information might include specific seasonal information about the use to be assessed, major regions on which the product is applied and how the product fits with other active ingredients in pest resistance management programs.
- The Registration Division (RD) should ensure that the appropriate restricted reentry interval (REI) is included on the proposed label.

9.2 Toxicology

- The requirement for the 90-day dermal toxicity study is not waived. As a condition of registration, HED recommends Nichino submit the dermal toxicity study with rats dosed up to the limit dose in an effort to better characterize long-term dermal exposure

- As a condition of registration, the dose range-finding studies mentioned in the 4 week inhalation study should be submitted to the Agency. It was stated that in a previously conducted study with groups of 3 rats/sex/concentration, deaths were observed after a single 6-hour exposure to 26 or 79 mg/m^3. In repeated dose studies, similar groups of rats tolerated a 4-day exposure at 11 mg/m^3 or 5 days at 3.6 mg/m^3

References:

Tolfenpyrad: Occupational Risk Assessment to Support Registration for Use of the New Active Ingredient on Ornamental Plants in Greenhouses. D366500, Z. Figueroa, June 3, 2010.

Appendices

Appendix A: Toxicology Assessment

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for non-food use for tolfenpyrad are in Table A1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1 Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21/28-Day Dermal	no	yes
870.3250	90-Day Dermal	yes	no
870.3465	90-Day Inhalation	no	---
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	no	yes
870.4100b	Chronic Toxicity (nonrodent)	no	yes
870.4200a	Oncogenicity (rat)	no	yes
870.4200b	Oncogenicity (mouse)	no	yes
870.4300	Chronic/Oncogenicity	no	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Mammalian Erythrocyte Micronucleus	no	yes
870.5550	Mutagenicity—Unscheduled DNA Synthesis	no	yes
870.5915	Mutagenicity—*In Vivo* Sister Chromatid Exchange	no	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	---
870.6100b	90-Day Neurotoxicity (hen)	no	---
870.6200a	Acute Neurotox. Screening Battery (rat)	no	---
870.6200b	90 Day Neurotox. Screening Battery (rat)	no	---
870.6300	Develop. Neuro	no	---
870.7485	General Metabolism	no	yes
870.7600	Dermal Penetration	no	yes
870.7800	Immunotoxicity	yes	yes

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity Profile -Tolfenpyrad				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute Oral -Rat	47457501	LD_{50} Males => 386 mg/kg bw LD_{50} Females =>150 mg/kg bw LD_{50} Combined =>239 mg/kg bw	II
870.1200	Acute Dermal-Rat	47457503	LD_{50} Males > 2000 mg/kg bw LD_{50} Females > 3000 mg/kg bw LD_{50} Combined > 2500 mg/kg bw	III
870.1300	Acute Inhalation-Rat	47447734	LC_{50} Males >2.21 mg/L LC_{50} Females >1.50 mg/L LC_{50} Combined >1.82 mg/L	III
870.2400	Acute Eye Irritation-Rabbit	47457505	Mildly irritating	III
870.2500	Acute Dermal Irritation-Rabbit	47457507	Slightly irritating	IV
870.2600	Skin Sensitization-Guinea Pig	47447740	Not Sensitizing	-

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Tolfenpyrad			
Type of Study/Guideline	**Study Title**	**MRID**	**Results**
870.3100	90-Day Oral Toxicity, Rat w/4 week recovery	47447743	Levels tested: 0, 15, 80, 160 ppm or 0/0, 0.9/1, 4.8/5.2, 9.3/9.3 mg/kg/day in males/females NOAEL (M/F) =15 ppm or 0.9/1 mg/kg/day LOAEL (M/F) = 80 ppm or 4.8/5.2 mg/kg/day, based on decreased body weight (5-9%), body weight gain (8-13%), and food consumption in both sexes; increased relative liver and kidney weight, hepatocellular hypertrophy and kidney hypertrophy, hyaline droplets in the kidney, brown color change in the liver.; brown color change in the harderian gland along with hypersecretion. Additionally at 160 ppm, decreased body weight (8-26%), body weight gain (35-41%) and food consumption; small sex organs (seminal vesicle, ovary, uterus, and vagina; ovarian and uterine atrophy and decreased ovarian weight.
870.3100	90-Day Oral Toxicity,	47463702 and	Levels tested: 0, 15, 100, 300 pm or 0/0, 2.4/3.0,

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Tolfenpyrad			
Type of Study/Guideline	**Study Title**	**MRID**	**Results**
	Mouse	47447801	15.9/20.2, 46.2/57.9 mg/kg/day in males/females NOAEL (M/F)-300 ppm or 46.2/57.9 mg/kg/day LOAEL (M/F)-not determined in main study; 600 ppm (104/126 mg/kg/day) based on decreased body weights, body weight gains, clinical signs (rough coats, hunched posture, ataxia, hypoactivity), and moribundity/mortality seen in 28 day oral study. Note: Decreased Body weight gain (42%) was observed at 300 ppm in the range-finding study; however, 600 ppm (the HDT) was selected as the LOAEL for the 90 day mouse study since no effects on body weight gain were seen in this study at 300 ppm.
870.3150	4-week Oral Toxicity, Dog (capsule)	47447805	Levels tested: 0, 1, 5, 10 mg/kg/day NOAEL (M/F) = 5 mg/kg/day LOAEL (M/F) = 10 mg/kg/day, based on abnormal feces and liver and kidney histopathology.
	13-week Oral Toxicity, Dog (capsule)	47447803	Levels tested: 0, 1, 5, 10 mg/kg/day NOAEL (M/F) = 10 mg/kg/day LOAEL (M/F) = Not determined
870.3150	13-week Oral Toxicity, Dog (capsule)	47447804	Levels tested: 0, 10, 30, 100 mg/kg/day NOAEL (M/F) = 10 mg/kg/day LOAEL (M/F) = 30 mg/kg/day, based on mortality (1/4 males); clinical signs (no defecation/watery feces, emaciation, decrease in spontaneous movement, and staggering gait); decreased body weights, body weight gains, and food consumption; and effects on the liver (increased cytoplasmic eosinophilia and centrilobular vacuolation in the hepatocytes) and in males, testes (atrophy) and kidney (vacuolization of tubular epithelium).
870.3200	21-Day Dermal	47447806	Levels tested: 0, 10, 50, 200 mg/kg/day NOAEL (M/F) = 200 mg/kg/day LOAEL (M/F) = not determined At ≥ 50 mg/kg/day, decreased body weight gain and food consumption observed.
870.3250	90-Day Dermal	No study Available: Waiver request submitted	
870.3465	4-Week Inhalation Toxicity, Rat	47447728	Levels tested: 0, 0.50, 2.0, 10 mg/m^3 or 0, 0.0005, 0.002, and 0.01 mg/L NOAEL = 10 mg/m^3 (EPA calculated 2.6 mg/kg/day) LOAEL = not determined Mortality observed at 26 mg/m^3 (EPA calculated 6.8 mg/kg/day) in range-finding study (not available).
870.3700a	Developmental Toxicity, Rat (Gavage)	47447809	Levels tested: 0, 1, 3, 4.5 mg/kg/day; GD 6-15) Maternal NOAEL =1mg/kg/day

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Tolfenpyrad			
Type of Study/Guideline	**Study Title**	**MRID**	**Results**
			Maternal LOAEL = 3 mg/kg/day, based on decreased body weight gains and food consumption Developmental NOAEL = 3 mg/kg/day Developmental LOAEL = 4.5 mg/kg/day, based on increased incidences of 14th ribs, decreased fetal body weights, and decreased number of ossified metacarpals.
870.3700b	Developmental Toxicity, Rabbit (Gavage)	47447811	Levels tested: 0, 1, 3, 6 mg/kg/day GD 6-18 Maternal NOAEL = 6 mg/kg/day Maternal LOAEL = 9 mg/kg/day. The maternal LOAEL was not established in the current study but was 9 mg/kg/day in the preliminary study (MRID 47447810) based on a single mortality, emaciation, and on decreased body weights, body weight gains, and food consumption Developmental NOAEL = 6 mg/kg/day Developmental LOAEL = 9 mg/kg/day. The developmental LOAEL was not established in the current study but was 9 mg/kg/day in the preliminary study based on increased early resorption and incidences of supernumerary coronary orifices, fusion of the ossification centers of the caudal vertebral bodies, 13th ribs, and delayed ossification of the manus
870.3800	2 Generation Reproduction, Rat (feeding)	47447817	Levels tested: 0, 0.75, 1.5, or 3.0 mg/kg/day. Parental NOAEL = 1.5 mg/kg/day Parental LOAEL = 3.0 mg/kg/day, based on decreased body weight and body weight gains, decreased motor activity, reddish tears, and prone position prior to death in two dams. Reproductive NOAEL= 1.5 mg/kg/day Reproductive LOAEL=3.0 mg/kg/day, based on decreased gestation index, increased gestation duration, abnormal parturition, and total litter loss Offspring NOAEL = 1.5 mg/kg/day Offspring LOAEL = 3.0 mg/kg/day, based on decreased pup viability and body weights, and delays in attainment of developmental landmarks (eye opening, pinna folding, surface righting reflex)
870.3800	1 Generation Reproduction, Rat (feeding)	47447816	Levels tested: 0, 15, 50, 100 ppm or 0/0, 0.86/0.92, 2.7/2.9, 4.8/4.4 mg/kg/day. Parental NOAEL = 15 ppm or 0.86/0.92 mg/kg/day Parental LOAEL = 50 ppm or 2.7/2.9 mg/kg/day, based on decreased body weight gains and food consumption during pre-mating, and on decreased body weights during gestation and lactation in the females. Reproductive NOAEL= 50 ppm Reproductive LOAEL= 100 ppm or 4.8/4.4, based on increased gestation duration

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Tolfenpyrad			
Type of Study/Guideline	**Study Title**	**MRID**	**Results**
			Offspring NOAEL = 15 ppm Offspring LOAEL = 50 ppm, based on decreased body weights and body weight gains in both sexes.
870.4100	Chronic Toxicity-1 Year, Dog (feeding)	47442818	Levels tested: 0, 1, 5, 10 (reduced from 20) mg/kg/day NOAEL (M/F) 5 mg/kg/day LOAEL (M/F) 10 mg/kg/day, based on mortality, vomiting, decreased body weights, body weight gains, food consumption,, increased serum alanine aminotransferase in the males, and microscopic liver findings in males and females
870.4200a	Carcinogenicity, 18-Month Mouse (feeding)	47463703	Levels tested: 0, 15, 150 ppm or 0, 2.2/2.8, 20.8/27.1 mg/kg/day in males/females; An additional group of 50 mice/sex/dose was treated similarly at a dose of 500 ppm for Weeks 1-12, 400 ppm for Weeks 13-19, and 300 ppm for Weeks 20-79 (60.9/75.9 mg/kg bw/day in males/females). The dose for the high group was adjusted twice due to observed toxicity (mortality). NOAEL (M/F) 15 ppm or 2.2/2.8 mg/kg/day LOAEL (M/F) 150 ppm or 20.8/27.1 mg/kg/day, based on moderate decreases in body weight (3-9%) and body weight gain (18%), food consumption, and clinical signs (increased incidence of ears missing in males and ear sores and scabs in females)
870.4200b	Chronic/Oncogenicity, 2-Year, Rat (feeding)	47463704	Levels tested: 0, 15, 40, 80 ppm or 0/0, 0.6/0.7, 1.5/1.9, and 3.1/3.8 mg/kg/day in males/females NOAEL (M/F) 15 ppm or 0.6/0.7 mg/kg/day LOAEL (M/F) 40 ppm or 1.5/1.9 mg/kg/day, based on decreased body weight, body weight gain, and food consumption of females, gross changes in the Harderian glands of males, and histopathological changes in the liver, kidney and mesenteric lymph nodes of females and the kidney of males.
870.5100	Technical (OMI-88) *In vitro* Bacterial Gene Mutation *(S. typhimurium/ E. coli)*/ mammalian activation gene mutation assay	47463705	Negative. There was no evidence of induced mutant colonies over background.
870.5100	Metabolite (OH-PT) *In vitro* Bacterial Gene Mutation *(S. typhimurium/ E. coli)*/ mammalian activation gene mutation assay	47447822	Negative. There was no evidence of induced mutant colonies over background.
870.5300	Technical (OMI-88)	47463706	Negative. There was no evidence of induced mutant colonies over background in the presence or absence of S9-activation.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Tolfenpyrad			
Type of Study/Guideline	**Study Title**	**MRID**	**Results**
	In Vitro Gene Mutation assay in mouse lymphoma cells		
870.5375	Technical (OMI-88) *In vitro* Mammalian Cytogenetics (Chromosomal Aberration Assay in Chinese Hamster Lung (CHL) cells)	47447824	Negative. There was no evidence of structural chromosome aberrations induced over background in the presence or absence of S9-activation. Note: cultures treated for 24 and 48 hours in the absence of S9 in Trial 2 resulted in a marked increase in the frequency of cells with numerical chromosome aberrations (predominantly polyploidy) that exceeded the historical control range. However, this effect decreased with an increase in dose. Similarly, a significant effect was only observed at the low-dose (10.1 µg/mL) during Trial 1 (24 hr, -S9). The biological significance of polyploidy *in vitro* is not completely understood at the present time. Therefore, this finding was not considered to be an adverse treatment-related effect. The positive controls induced the appropriate response in the presence and absence of S9 in both trials.
870.5375	Metabolite (OH-PT) *In vitro* Mammalian Cytogenetics (Chromosomal Aberration Assay in Chinese Hamster Lung (CHL) cells)	47447826	Negative. There was no evidence of structural chromosome aberrations induced over background in the presence or absence of S9-activation.
870.5395	Technical (OMI-88) *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus Assay	47447827	Negative. There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any treatment time.
Non-guideline	Technical (OMI-88) Cell Cycle Kinetics Assay	47463707	The purpose of this study was to explain the polyploidy observed in a previously conducted Chinese hamster lung chromosome aberration study (MRID 47447824). In the absence of S9-activation, Tolfenpyrad caused cell cycle delay after exposure for as little as 3 hours and polyploidy after as little as 6 hours exposure. The polyploidy observed in the previous chromosome aberration study was likely due to the inhibition of cell cycle progression.
870.6200a	Acute Neurotoxicity, Rat (gavage)	47447831	Levels tested: 0, 20, 40, 60 mg/kg/day in males and 0, 10, 20, or 40 mg/kg/day in females. NOAEL (M/F) = 10 mg/kg/day LOAEL (M/F) = 20 mg/kg/day, based on decreases in body weight, body weight gain and food consumption in females.
870.6200b	Subchronic Neurotoxicity, Rat (feeding	47447830	0, 15, 40, 80 ppm or 0/0, 1/1.2, 2.7/3.2, 5.4/6 mg/kg/day

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Tolfenpyrad			
Type of Study/Guideline	**Study Title**	**MRID**	**Results**
			NOAEL (M/F) =40 ppm or 2.7/3.2 mg/kg/day LOAEL (M/F) = 80 ppm or 5.4/6 mg/kg/day, based on decreased body weights, body weight gains, and food consumption
870.6300	Developmental Neurotoxicity, Rat	No study Available: Waiver request submitted	
870.7485	Metabolism, Rat	47447837, 47447836, 47447834, 47447833, and 47447835	The test compound was rapidly absorbed and excreted. Total recoveries ranged from 91.3-99.6% of the administered dose (AD) across all groups and in both sexes. Feces were the predominant route of excretion. Across all single dose groups, 88.2-93.2% AD was excreted in the feces and 1.7-3.0% AD was eliminated in the urine. Negligible amounts of radioactivity were recovered in the expired air and cage wash, both accounting for ≤0.1% AD. In the bile duct-cannulated rats at 48 h post-dosing, the majority of radioactivity was excreted in the bile (51.3-69.5% AD), with minor amounts eliminated in the feces (3.5-8.3% AD) and urine (0.7-3.0% AD), indicating that bile was the primary route of excretion for the absorbed test material. Absorption (defined as radioactivity found in the bile, urine, cage wash, and carcass) was greater in males (72.8-77.8% AD) than in females (57.9-69.4% AD). Females also had more radioactivity remaining in the gastrointestinal tract, and the amount remaining increased with dose.
870.7600	Dermal Penetration, Rat	47447839	At 24 hours in the 1 g/L group, the dermal absorption is 13%.
870.7800	Developmental Immunotoxicity, Rat (feeding)	47447840	Levels tested: 0, 0.75, 3 mg/kg/day Maternal NOAEL = 0.75 mg/kg/day Maternal LOAEL = 3 mg/kg/day, based on decreased body weight (up to 10%), body weight gain (up to 36%), and food consumption in the P generation Offspring NOAEL = 0.75 mg/kg/day Offspring LOAEL = 3 mg/kg/day, based on decreased survival, body weight, and body weight gains; increased incidence of blackish abdominal cavity and dark green abnormal intestinal content; and decreased thymus and spleen weights in the F1 and/or F2 generations <u>Note:</u> No treatment-related effects noted on the immune system.
Non guideline	*In vitro* metabolism	47447838	Total recovery was 91.0-108.1% of the radioactivity added to the incubations, of which the parent compound accounted for 10.2-12.4%. Only 1.4-1.9% of the radioactive residues were found in

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Tolfenpyrad			
Type of Study/Guideline	**Study Title**	**MRID**	**Results**
			unidentified compounds; the remaining approximately 88% of the isolated metabolites were identified. In addition to the parent, a total of 17 metabolites were identified. The primary metabolite was OH-PT-CA (24.5-32.4%); other major metabolites included PT-CA (13.4-16.2%), CO-PT-CA (9.3-13.2%), OH-PT (7.6-8.4%), PT-OH (6.7-7.7%), and OH-PT-OH (3.8-5.3%). The other metabolites were present at <5% of the total incubation dose. The main metabolic pathways included the oxidations of the methyl moiety of T-CH_3 and ω-1 carbon of CH_3CH_2-P. The oxidation of these two carbons resulted in the formation of the hydroxylated metabolites PT-OH, OH-PT, and OH-PT-OH. Further oxidation leads to the metabolites PT-CHO, PT-CA, OH-PT-CA, CO-PT, CO-PT-OH, and CO-PT-CA. Other metabolic pathways include the bond cleavage of the amide and methylene moieties, the demethylation of N-CH_3, or the formation of the vinyl group after hydroxylation of CH_3CH_2-P.

A.3 Executive Summaries

Oral Subchronic Toxicity Study-Rat; OPPTS 870.3100

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRID 47447743), Tolfenpyrad (OMI-88; 99.33% a.i.; Lot No. 6D-01-2) was administered in the diet to Fischer 344 rats (10/sex/dose) at doses of 0, 15, 80, or 160 ppm (equivalent to 0/0, 0.9/1.0, 4.8/5.2, and 9.3/9.3 mg/kg/day for males/females) for 13 weeks. Additionally 6 rats/sex were similarly treated for 13 weeks at 0 or 160 ppm and then subsequently allowed 4 weeks of control diet (recovery period).

No treatment-related effects were observed on mortality, clinical signs, ophthalmoscopic examinations, or urinalysis.

Decreased body weights, body weight gains, and food consumption were noted in the 80 and 160 ppm groups and decreased food efficiency was noted in the 160 ppm group. Decreased ($p<=0.05$) body weights were generally noted at Weeks 2-13 in the 80 ppm group (decr 4-9%) and throughout treatment in the 160 ppm group (decr 8-26%). Decreased ($p<=0.01$, except as noted) body weight gain was noted for the overall treatment period (Weeks 0-13) in the 80 ppm males (↓8%; not significant) and females (decr 13%) and the 160 ppm group (decr 35-41%). In males, food consumption (g/rat/day) was decreased ($p<=0.05$) in the 80 ppm group (decr 6-15%) for 5-6 of the 13 weeks. Decreased ($p<=0.05$) food consumption was observed throughout treatment in the 160 ppm group (decr 12-39%). The total mean food consumption for the treatment period was reduced by 5-10% in the 80 ppm group and by 23-31% in the 160 ppm `the 13 weeks by sex and determined that the grand mean was decreased by 17-20% at 160 ppm.

Decreased ($p<=0.05$) leukocyte counts were noted in the 80 and 160 ppm females at Week 14 (decr 27-29%). The adversity of this effect was considered marginal due to the magnitude of change.

At 160 ppm, the following sex organs were small: seminal vesicle, ovary, uterus, and vagina. Microscopically, increased incidences of slight ovary and uterus atrophy were observed at 160 ppm. Decreased ($p<=0.01$) relative ovary weight was also noted (decr 20%).

The following differences were observed in the clinical chemistry parameters of the 160 ppm group compared to the controls at Week 14: (i) decreased triglycerides in the males; (ii) increased potassium in both sexes; (iii) increased inorganic phosphorus in both sexes; (iv) increased urea nitrogen in females; (v) increased glucose in females; and (vi) increased γ-glutamyl transferase in females.

In the 80 and 160 ppm groups, increased relative to body liver weights were noted. In the 160 ppm group, increased incidence of brownish color was noted grossly in the liver, and an increased incidence of increased slight, diffuse hepatocellular hypertrophy was noted microscopically in males and females at 80 and 160 ppm. In both sexes of the 80 and 160 ppm groups, increased relative to body kidney weights were noted. Increased incidences of slight hyaline droplets in the kidney in the 80 and 160 ppm males and slight proximal tubular

epithelium hypertrophy in the kidney in the 80 and 160 ppm females were observed. In the 80 and 160 ppm group, increased incidence of brownish color and slight hypersecretion was observed in the Harderian gland.

In general, partial or complete recovery occurred for all findings during the recovery period.

The LOAEL is 80 ppm (equivalent to 4.8/5.2 mg/kg/day in males/females), based on decreased body weights, body weight gains, and food consumption in both sexes. Additionally, increased relative liver and kidney weights, hepatocellular hypertrophy, brown color change in the liver; hyaline droplets in the kidney; brown color change in the harderian gland along with hypersecretion. The NOAEL is 15 ppm (equivalent to 0.9/1.0 mg/kg/day in males/females).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100; OECD 408) for a subchronic oral toxicity study in the rat.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided.

Oral Subchronic Toxicity Study-Mouse; OPPTS 870.3100

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRID 47463702), Tolfenpyrad (99.33% a.i.; Lot No. 6D-01-2) was administered in the diet to 10 CD-1 mice/sex/dose at dose levels of 0, 15, 100, or 300 ppm (equivalent to 0/0, 2.4/3.0, 15.9/20.2, and 46.2/57.9 mg/kg/day in males/females) for 13 weeks.

No adverse, treatment-related effects were observed on mortality, clinical signs, body weight, body weight gains, food consumption, food efficiency, ophthalmology, hematology, clinical chemistry, urinalysis, organ weights, or gross or microscopic pathology.

During 4 of the 13 weeks, minor decreases ($p<=0.05$) in food consumption were observed in the 300 ppm males (decr 10-12%), and a minor decrease ($p<=0.05$) of 8% was noted in overall (Weeks 1-13) food consumption. These decreases in food consumption did not significantly ($p>0.05$) effect body weight or body weight gain.

The LOAEL was not established. The NOAEL was 300 ppm (equivalent to 46.2/57.9 mg/kg/day in males/females), the highest dose tested.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100; OECD 408) for a subchronic oral toxicity study in the mouse. Although the LOAEL was not established and the limit dose was not tested, this study was considered acceptable based on an acceptable dose-selection rationale.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

Oral Subchronic Toxicity Study-Dog; OPPTS 870.3150

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRID 47447803), OMI-88 (Tolfenpyrad, 99.33% a.i., Batch No. 6D-01-2) was administered to 4 Beagle dogs/sex/dose via gelatin capsule at dose levels of 0, 1, 5 or 10 mg/kg/day for 13 weeks.

No effects of treatment were observed on mortality, body weight, body weight gain, food consumption, food efficiency, ophthalmological examinations, hematology, clinical chemistry, urinalysis, absolute and relative organ weights, or gross or microscopic pathology.

Vomiting was observed at all doses in 2-3 males and 3-4 females, as well as 1 dog of each sex in the control groups. The total number of days of vomiting among treated animals (# observed out of a possible 92/93 days, M/F) was 6-15 in the males and 6-33 in the females, compared to 1-3 days for affected controls. Soft feces was observed in all males at 5 and 10 mg/kg/day (vs. 1/4 controls) with the total number of days being 16-23 treated vs. 2 controls). These findings were first observed during study Week 1, but the report did not indicate on which days. Additionally, mucous feces were noted in one 10 mg/kg/day female on 12 days during treatment. These findings may have reflected irritation to the gastrointestinal lining from a bolus (capsule) dose. Although vomiting and abnormal feces were observed more frequently in the treated groups compared to the controls, these findings were not accompanied by other clinical signs of toxicity and did not compromise food consumption, food efficiency, bodyweights, or body weight gains of the animals. Therefore, these findings were not considered adverse. **The LOAEL was not observed (>10 mg/kg/day), and the NOAEL is 10 mg/kg/day.**

This study is classified **acceptable/guideline**, and in conjunction with another 13-week oral toxicity study in dogs that establishes a LOAEL (MRID 47447804, reviewed concurrently in separate DER), fulfills the guideline requirement (OPPTS 870.3150; OECD 409) for a subchronic toxicity study in dogs.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided. No Flagging statement was provided.

Oral Subchronic Toxicity Study-Dog; OPPTS 870.3150

EXECUTIVE SUMMARY: In this subchronic oral toxicity study (MRID 47447804), 4 beagle dogs/sex/group were administered Tolfenpyrad (99.33% a.i.; Lot #6D-01-2) daily via capsule at doses of 0, 10, 30 or 100 mg/kg/day for 13 weeks. The study was conducted at higher doses than a previous 13-week oral dog study (MRID 47447803) to establish a clear LOAEL.

There were no treatment-related effects on ophthalmoscopy, hematology or organ weights.

In the 30 mg/kg/day group, one male (#3002) died on Day 90. In the 100 mg/kg/day group, one male (#4001) died on Day 13, and two females (# 4101 and 4103) died on Day 23. Additionally in this group, male #4004 and female #4102 were euthanized *in extremis* on Days 41 and 23,

respectively. The remaining two males and one female in this group exhibited clinical signs such as no feces, emaciation, and decreased body weight and food consumption. Therefore, these surviving animals (#4002, 4003, and 4104) were terminated on Day 49.

In all of the treated groups, salivation, vomiting and fecal abnormalities (soft feces, mucous feces, feces mixed with test material) were noted. These findings were observed with greater incidence and frequency at the higher two doses. Additionally at 30 and 100 mg/kg/day, incidences of no defecation, emaciation, decrease in spontaneous movement, and staggering gait were found in the males; and watery feces were observed in the females. These findings were reported in all dose groups during the first week, but it could not be determined from the individual animal data presentation in the study report whether they were observed on the initial day of dosing. At 100 mg/kg/day, mydriasis, lateral position, miosis and hypothermia were noted in the males; and emaciation, decrease in spontaneous movement, staggering gait and mydriasis were observed in the females (by Week 4). In general, these findings were dose-dependently increased in incidence and/or frequency.

At 100 mg/kg/day, body weights were decreased by 5-34% compared to controls in the males and by 8-39% in the females for Weeks 1 through 6. The magnitude of these differences became greater with time. Food consumption was decreased by 4-88% compared to controls during Weeks 2 through 7 in the males and by 15-76% during Weeks 1-7 in the females.

At 30 mg/kg/day, body weights in the males were decreased by 6-14% compared to controls during Weeks 7 through 13, with only minor decreases of 1-2% prior to Week 7. In the females at this dose, body weights were decreased by 3-7% throughout the study. Body weight gains for the overall (Weeks 0-13) study were 55% lower than controls in the males and 18% lower in the females. At 30 mg/kg/day, food consumption was 7-38% lower than controls in the males from Weeks 6 through 13. Only minor sporadic differences in food consumption were noted in the 30 mg/kg/day females and in both sexes at 10 mg/kg/day.

At 10 mg/kg/day, body weights were only minimally decreased (1-5%). Furthermore, the decreases in body weights in the males were sporadic. Overall body weight gains were 18% lower than controls in the males and 27% lower in the females.

Several changes in clinical chemistry indicated the reduced nutritional status of the animals, resulting from decreased food consumption, including decreased alkaline phosphatase at 30 and 100 mg/kg/day in both sexes and decreased triglycerides in all treated groups in the females. Albumin and albumin/globulin ratio were increased and α_1, β_1, and β_2 globulins were decreased in the 100 mg/kg/day females. The increase in albumin may indicate dehydration; whereas the decreases in globulins corroborate effects on the liver.

Blood urea nitrogen was increased by 64% at 30 mg/kg/day at Week 13 and by 33 and 208% in the 100 mg/kg/day males at Weeks 4 and 7, respectively. Urine volume was decreased by 62-73% in the 100 mg/kg/day males and females at Week 7.

Atrophy of the thymus was noted at gross necropsy in the one male at 30 mg/kg/day that died

(#3002) and in two males (#4002 and 4003) and one female (#4104) at 100 mg/kg/day.

The following treatment-related microscopic lesions (# affected vs 0 controls) were observed at 30 and 100 mg/kg/day: (i) increased cytoplasmic eosinophilia of hepatocyte in the 30 mg/kg/day males (2) and females (1) and 100 mg/kg/day males (4) and females (4); (ii) centrilobular vacuolation in hepatocytes in the 30 mg/kg/day males (1) and 100 mg/kg/day males (2) and females (2); (iii) atrophy of the thymus in the 30 mg/kg/day males (1) and 100 mg/kg/day males (3) and females (3); (iv) atrophy of the submandibular lymph node in the 30 mg/kg/day males (1) and 100 mg/kg/day males (3) and females (2); (v) atrophy of the mesenteric lymph node in the 30 mg/kg/day males (1) and 100 mg/kg/day males (4) and females (2); (vi) vacuolation in the tubular epithelium in the kidneys in the 30 mg/kg/day males (1) and 100 mg/kg/day males (2) and females (1); (vii) atrophy of the Peyer's patch in the ileum in the 30 mg/kg/day males (1) and 100 mg/kg/day males (4) and females (2); (viii) atrophy of the seminiferous tubules in the testes at 30 mg/kg/day (3) and 100 (4) mg/kg/day; (ix) decrease in the number of sperm in the lumen of the epididymis at 30 mg/kg/day (1) and 100 (1) mg/kg/day; (x) cell debris in the lumen of the epididymis at 30 mg/kg/day (1) and 100 (2) mg/kg/day; and (xi) atrophy of the prostate at 30 mg/kg/day (1) and 100 (2) mg/kg/day.

Additionally at 100 mg/kg/day, the following microscopic lesions were found (compared to 0 controls): (i) brown pigmentation in Kupffer's cell in 1 female; (ii) hypocellularity of the bone marrow in 2 males and 1 female; (iii) focal degeneration and hemorrhage in the cerebrum in 1 male and 1 female; (iv) focal degeneration in the cerebellum in 1 male and 1 female; (v) focal hemorrhage in the cerebellum in 1 female; (vi) focal hemorrhage in the heart in 1 male and 1 female; (vii) sublingual gland atrophy 1 male; (viii) focal hemorrhage in the lungs in 1male; (ix) lung congestion in 1 female; and (x) atrophy of the ovaries in 1 female.

The LOAEL is 30 mg/kg/day based on: mortality (1/4 males); clinical signs (no defecation/watery feces, emaciation, decrease in spontaneous movement, and staggering gait); decreased body weights, body weight gains, and food consumption; and effects on the liver (increased cytoplasmic eosinophilia and centrilobular vacuolation in the hepatocytes) and in males, testes (atrophy) and kidney (vacuolization of tubular epithelium). The NOAEL is 10 mg/kg/day.

This study is classified **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3150; OECD 409) for a subchronic oral toxicity study in dogs.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging and Quality Assurance statements were provided.

Dermal Subchronic (28-day) Toxicity Study-Rat; OPPTS 870.3200

EXECUTIVE SUMMARY: In a repeated-dose dermal toxicity study (MRID 47447806), Tolfenpyrad (99.5% a.i., Lot #: 365-65A) was applied neat (moistened with 0.2 mL deionized water) to the shaved intact skin of 10 Sprague-Dawley rats/sex/dose at dose levels of 0, 10, 50, or 200 mg/kg/day, 6 hours/day for 21 consecutive days.

No adverse compound-related effects were observed in mortality, clinical signs of toxicity, body weight, ophthalmoscopic exams, hematology, clinical chemistry, absolute or relative organ weights, or gross or microscopic pathology in either sex. No treatment-related dermal effects were observed at any dose in either sex. Slight dermal irritation was observed at 50 and 200 mg/kg/day; however, this finding was not considered adverse.

In the 50 mg/kg/day females, absolute food consumption was decreased ($p<=0.05$) by 9% during Days 15-21 and by 6% overall (Days 1-21). Additionally in these animals, non-statistically significant decreases in body weight were noted at Days 15 and 21 (decr 4-7%), overall (Days 1-21) body weight gain was decreased ($p<=0.01$) by 42% compared to controls.

In the 200 mg/kg/day females, absolute food consumption was decreased ($p<=0.05$) by 11% during Days 15-21 and by 7% overall. Additionally in these animals, non-statistically significant decreases in body weight were noted at Days 15 and 21 (decr 5-8%), and overall body weight gain was decreased ($p<=0.01$) by 44% compared to controls.

The reviewers disagree with the Sponsor that the NOAEL was 200 mg/kg/day. The animals were of the appropriate age (approximately 8 weeks old) at the beginning of the study, and the controls displayed expected levels of body weight gain. These statistically significant decreases in overall body weight gain in the females were considered biologically significant.

The LOAEL is 50 mg/kg/day, based on decreases in body weight gain and food consumption in the females. The NOAEL is 10 mg/kg/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for a 21-day dermal toxicity study (OPPTS 870.3200; OECD 410) in rats.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

Subchronic Inhalation Study-Rat; OPPTS 870.3465

EXECUTIVE SUMMARY: In a subchronic inhalation toxicity study (MRID 47447728), Tolfenpyrad (99.5% a.i., Lot #365-65A) was administered as an aerosol dust in air to 10 Sprague-Dawley rats/sex/concentration by nose-only exposure at concentrations of 0 (air), 0.50, 2.0, or 10 mg/m^3 (equivalent to analytical concentrations of 0, 0.0005, 0.002, and 0.01 mg/L, respectively) for 6 hours per day, 5 days/week during a 4-week period, for a total of 20 exposure days.

There were no mortalities or clinical signs of toxicity. Furthermore, no treatment related effects were observed on body weights, body weight gains, food consumption, food efficiency, ophthalmology, clinical chemistry, urinalysis, gross pathology, or histopathology.

At 10 mg/m^3, the number of white blood cells was decreased by 24% ($p<=0.05$) in the females

compared to controls. Corresponding decreases were observed in all white cell types in these animals, with significant (p<=0.05) decreases in the numbers of lymphocytes (decr 23%), monocytes (decr 29%), eosinophils (decr 57%), and basophils (decr 50%), and a non-significant decrease in the number of neutrophils (decr 27%). Additionally, the number of large unstained cells was significantly (p<=0.05) decreased by 25% in the females at this concentration. In the absence of corroborating findings, these decreases were considered to be of equivocal toxicological importance. These decreases were within historical control range and were not observed in males.

Absolute liver weights and liver weights relative to body weight and to brain weight were increased by 15-17% (p<=0.05) in the 10 mg/m^3 females. Minimal diffuse hepatocellular hypertrophy was found in 2/10 males and 3/10 females at this concentration compared to 0 controls. Although treatment-related, the increased liver weights and hepatocellular hypertrophy were considered to be an adaptive response to the test material and not adverse at this concentration.

The LOAEL was not observed. The NOAEL is 10 mg/m^3 (equivalent to an analytical concentration of 0.01 mg/L).

Although a LOAEL was not observed, an acceptable concentration-selection rationale was provided. In the previously conducted dose range-finding studies with groups of 3 rats/sex/concentration, deaths were observed after a single 6-hour exposure to 26 or 79 mg/m^3. In repeated dose studies, similar groups of rats appeared to tolerate a 4-day exposure at 11 mg/m^3 or 5 days at 3.6 mg/m^3. Given the fact that mortality was observed at 26 mg/m^3 after a single 6-hour exposure, it was reasonable for the Sponsor to select 10 mg/m^3 as the high concentration for a 28-day study (20 exposure days). Because only adaptive effects were noted in the liver in both sexes and equivocal decreases in white blood cells were seen in the females at 10 mg/m^3 in the current study, the reviewers recommend that any future 28-day study be conducted in the range 10 mg/m^3 to 26 mg/m^3.

At the request of the Agency, this study was conducted for 4 weeks, instead of the 13 weeks required by Guideline OPPTS 870.3465. Aside from the different study duration, this study was conducted in accordance with Guideline OPPTS 870.3465.

This 4-week study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.3465; OECD 413) for a subchronic inhalation study in the rat.

COMPLIANCE - Signed and dated Data Confidentiality, GLP Compliance and Quality Assurance statements were provided.

Developmental Toxicity Study-Rat; OPPTS 870.3700a

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 47447809), tolfenpyrad (99.33%; Lot # 6D-01-2) in 0.5% carboxymethylcellulose (CMC) was administered via daily oral gavage in a dose volume of 10 mL/kg to 24 naturally-mated presumed pregnant Sprague-

Dawley rats/dose group at doses of 0, 1, 3, or 4.5 mg/kg/day from gestation days (GD) 6-15. On GD 20, all surviving maternal rats were euthanized; each dam's uterus was removed via cesarean section and its contents examined. The fetuses were examined for external, visceral, and skeletal malformations and variations. Another study report (MRID 47447812) stated that it included additional fetal examination data; however, these data were identical to the data for the visceral and skeletal examinations of the fetuses already presented in the definitive study report (denoted as "amended"). An addendum (MRID 47447813) was included to include summary and individual necropsy findings and data on maternal body weights and body weight gains corrected for total live fetal weight (in lieu of gravid uterine weight); these data are incorporated in appropriate sections within the body of this DER. Another addendum (MRID 47447815) was submitted to assess the possible effect of the shorter administration period on the study conclusions; this information is included in an appendix in this DER.

All maternal animals survived until scheduled termination. No clinical signs of toxicity were noted in any of the dams. Aside from a single dam at 4.5 mg/kg/day with a mammary gland nodule, no gross abnormalities were found in any animal at any dose level. This finding was considered incidental to treatment.

At 3 and 4.5 mg/kg/day, body weight gains were dose-dependently decreased ($p<=0.01$) by 57-113% for GD 6-9, by 29-69% for GD 6-12, and by 24-47% for the overall (GD 6-15) treatment interval. Additionally at 4.5 mg/kg/day, body weight gains were decreased by 19% compared to controls for GD 6-20 and by 21% for GD 0-20 (when corrected for the total weight of the live fetuses). Body weights were decreased by 7-9% ($p<=0.01$) at 4.5 mg/kg/day beginning on GD 9 and continuing throughout the remainder of the study. Maternal food consumption was dose-dependently decreased ($p<=0.01$) by 9-12% at 3 mg/kg/day and by 28% 4.5 mg/kg/day on GD 9 and GD 12. There were no treatment-related effects on body weights, body weight gains, or food consumption at 1 mg/kg/day.

The maternal LOAEL is 3 mg/kg/day based on decreased body weight gains and food consumption. The maternal NOAEL is 1 mg/kg/day.

There were no abortions, premature deliveries, complete litter resorptions, or dead fetuses. There were no effects of treatment on the numbers of litters, live fetuses, early resorptions, or late resorptions. Furthermore, sex ratio and post-implantation losses in the treated groups were comparable to controls.

At 4.5 mg/kg/day, fetal body weights were decreased by 7-9% compared to controls. The mean number of ossified metacarpi at 4.5 mg/kg/day (6.43) was significantly ($p<=0.05$) lower than controls (7.00). The numbers of ossified cervical vertebrae, sternebrae, metatarsi, and sacral and caudal vertebrae of the treated groups were comparable to controls.

No external or visceral variations were noted. Incidences of 14^{th} ribs, a variation, were increased ($p<=0.05$) at 4.5 mg/kg/day (16 fetuses; 5 litters) compared to controls (1 fetus). There were no other treatment-related skeletal variations.

At 4.5 mg/kg/day, one fetus (#L06 from Dam #50405) had microcephaly and anophthalmia observed externally, corresponding to holoprosencephaly observed viscerally. Additionally at this dose, abnormal origin of the right subclavian artery was noted in a single fetus. Although no historical control data were provided, it is unlikely that these findings were due to treatment because only a single fetus per each finding was affected.

The developmental LOAEL is 4.5 mg/kg/day based on increased incidences of 14th ribs, decreased fetal body weights, and decreased number of ossified metacarpals. The developmental NOAEL is 3 mg/kg/day.

This study is classified **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.3700a; OECD 414) for a developmental toxicity study in rats.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

Developmental Toxicity Study-Rabbit; OPPTS 870.3700b

EXECUTIVE SUMMARY: : In a developmental toxicity study (MRID 47447811), tolfenpyrad (99.33%; Lot # 6D-01-2) in 0.5% carboxymethylcellulose (CMC) was administered via daily oral gavage in a dose volume of 5 mL/kg to 16 artificially inseminated Japanese White rabbits/dose group at doses of 0, 1, 3, or 6 mg/kg/day from gestation days (GD) 6-18. On GD 28, all surviving maternal rabbits were euthanized; each doe's uterus was removed via cesarean section and its contents examined. The fetuses were examined for external, visceral, and skeletal malformations and variations.

In the 3 mg/kg/day group, one animal (# 50312) died on GD 28. Although no clinical signs of toxicity were noted in this animal prior to death, food consumption was decreased on GD 9, and essentially no food was eaten for the remainder of the study. Thus, body weights were consistently decreased after GD 9. Lung congestion, yellowing of the liver, and small spleen were noted during the gross necropsy. Microscopic findings of lung congestion, diffuse fat accumulation in the hepatocytes, and atrophy of the spleen corresponded to the gross lesions noted in this animal. Additionally, fat accumulation was found in the renal tubule epithelium at the corticomedullary junction of the kidney. In contrast to the investigator's conclusions, the reviewers do not consider this death to be due to treatment because no mortality was observed at 6 mg/kg/day in this study or in the preliminary study (MRID 47447810). Furthermore, the gross and microscopic findings noted in the lung, spleen, and kidney in this dam were not found in any of the maternal animals in the range-finding study (including one dam from the 9 mg/kg/day that died); and yellowish liver was noted in a single 3 mg/kg/day dam in the range-finding study, with no such findings at higher doses.

In the 6 mg/kg/day group, one dam (# 50406) delivered prematurely on GD 27. No changes in clinical signs were observed in this animal on the previous day, and no gross abnormalities were found at necropsy. In the range-finding study, premature delivery was noted in a single dam at 6 mg/kg/day and another at 9 mg/kg/day. It is important to note that all three of these premature

deliveries occurred just prior to the expected day of parturition (on GD 27 or GD 28), and that no abortions or dead fetuses were observed.

At 3 mg/kg/day, food consumption was decreased by 11-27% from GD 12 through GD 18. However, these decreases were not statistically significant and did not result in decreased body weights or body weight gains.

At 6 mg/kg/day, food consumption was significantly ($p<=0.01$) decreased by 38% compared to controls on GD 9. Although food consumption remained decreased by 13-28% throughout the remainder of the treatment period, these decreases were not statistically significant. Furthermore, body weights were only decreased by 2-5% throughout the treatment period, with a mean body weight loss of 9 grams at this dose compared to a mean body weight gain of 99 grams in the controls for the treatment period (GD 6-18). Therefore, in contrast to the investigators' conclusions, these decreases in food consumption, body weights, and body weight gains were not considered adverse because they were minor and not biologically or statistically significant.

In the preliminary study (see Appendix of this DER), one dam died at 9 mg/kg/day and another was emaciated. Maternal body weights, body weight gains, and food consumption were substantially decreased at this dose and considered to be adverse effects of treatment.

The maternal LOAEL was not established in the current study but was 9 mg/kg/day in the preliminary study based on a single mortality, emaciation, and on decreased body weights, body weight gains, and food consumption. The maternal NOAEL is 6 mg/kg/day.

There were no abortions or dead fetuses and no effects of treatment on the numbers of litters, early resorptions, or late resorptions. Fetal body weights and sex ratio in the treated groups were comparable to controls. The mean number of live fetuses/dam was decreased by 21% at 6 mg/kg/day compared to controls. However, this decrease corresponded to a decrease of 18% in the mean number of implantations/dam in this dose group. Because implantation occurs prior to the initiation of treatment, these decreases were unrelated to exposure to the test material. Complete litter resorptions occurred in 0, 1, 1, and 2 litters at 0, 1, 3, and 6 mg/kg/day, respectively. In the 1 mg/kg/day litter (#50204), 3 mg/kg/day litter (#50301), and one of the 6 mg/kg/day litters (#50403), only a single implantation occurred, which resulted in an early resorption. It is unlikely that the loss of these single implantations was due to treatment. The other complete litter resorption at 6 mg/kg/day (#50405) was characterized by 9 implantations resulting in early resorptions. Post-implantation loss was dose-dependently increased in all treated groups (12.70-16.67%) compared to controls (9.01%). Because the mean numbers of resorptions/dam in the treated groups were comparable to controls, the increased post-implantation loss is likely a reflection of the complete litter resorptions in these groups.

Treatment with the test material did not affect growth or development of the fetuses. Fetal body weights were comparable to controls. The number of ossified cervical vertebrae, sternebrae, metacarpi, metatarsi, and sacral and caudal vertebrae of the treated groups were comparable to controls. There were no treatment-related variations or malformations.

In the preliminary study at 9 mg/kg/day, post-implantation loss and the number of early resorptions were increased, largely attributed to the complete litter resorption of an emaciated dam (# E05). Live litter size was decreased as a result. In the fetuses, increased incidences of fetuses with supernumerary coronary orifices, fusion of the ossification centers of the caudal vertebral bodies, and 13th ribs were observed. The number of ossified bones in the medial manus was decreased.

The developmental LOAEL was not established in the current study but was 9 mg/kg/day in the preliminary study based on increased early resorption and incidences of supernumerary coronary orifices, fusion of the ossification centers of the caudal vertebral bodies, 13th ribs, and delayed ossification of the manus. The developmental NOAEL is 6 mg/kg/day.

This study is classified **acceptable/guideline** and, in conjunction with the preliminary study (MRID 47447810), satisfies the guideline requirement (OPPTS 870.3700b; OECD 414) for a developmental toxicity study in rabbits.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided.

Developmental Immunotoxicity in rats; Non-guideline

EXECUTIVE SUMMARY: In a developmental immunotoxicity study (MRID 47447840), presumed pregnant Sprague-Dawley rats (15/dose) were administered Tolfenpyrad (OMI-88; 99.33% a.i.; Lot no. 6D-01-2) as dietary admixtures at doses of 0, 0.75 or 3 mg/kg/day. The dietary formulations were presented to the P generation dams beginning on GD 0 and continuing through LD 21, after which the dams were sacrificed. The F1 generation rats were offered the dietary formulations at the same concentrations as their parents beginning on PND 21. Offspring following weaning, one pup/sex/litter was selected to continue on study when possible in both F1 and F2 generations. F1 and F2 males were treated daily from PND 21 until their scheduled necropsy at either 3 (F1 only) or 10 weeks of age (F1 and F2). The F1 parents were fed the test diets for at least 10 weeks prior to mating to produce the F2 litters.

For maternal toxicity, mortality, clinical signs, body weight, body weight gain, food consumption, and gross pathology were evaluated in P and selected F1 and F2 adults. Additionally, in the P and F1 adults, the number of implantations, uterine contents, live and stillborn pups, litter size, and pup viability were evaluated. For offspring toxicity, the following parameters were evaluated in selected F1 and F2 pups: viability, clinical signs, body weight, body weight gain, organ weights (brain, thymus, and spleen), and gross pathology. Immunotoxicity parameters were evaluated in selected F1 and F2 adults (males only) including total leukocytes, leukocyte differential counts, spleen and thymus weights and cellularity, percentage distribution and number of lymphocyte subpopulations using surface markers, serum titer of anti-SRBC (sheep red blood cells) antibody, and delayed-type hypersensitivity (cell-mediated immunity to keyhole limpet hemocyanin, KLH).

For maternal toxicity, no treatment-related effects were observed on mortality, clinical signs, gross pathology, or reproduction in the P and F1 generations. In the P generation dams, decreased body weights (↓4-10%) were observed in the 3 mg/kg/day group at GD 7, 14, and 20 and at LD 0, 4, and 7. Maternal cumulative body weight gains were decreased at GD 7, 14, and 20 (↓20-36%), but increased body weight gains were observed at LD 7, 14, and 21 (↑62-145%). Decreased food consumption (g/rat/day) was noted throughout gestation and lactation (↓9-22%). No adverse, treatment-related effects were noted on body weights, body weight gains or food consumption in the F1 adults.

The maternal LOAEL is 3 mg/kg/day, based on decreased body weight, body weight gain, and food consumption in the P generation. The maternal NOAEL is 0.75 mg/kg/day.

Offspring toxicity was observed at 3 mg/kg/day. Decreased numbers of offspring at birth and live offspring at birth (decr 12-13%) were noted relative to controls in the F1 generation and a decreased number of live offspring on PND 4 was noted before culling. Additionally, increased incidences of death and cannibalism were observed. A blackish abdominal cavity was noted from PND 1-6 in 3-34 pups in 9 litters vs 0 controls in the F1 generation and from PND 1-4 in 1-4 pups in 2 litters vs 0 controls in the F2 generation.

Mean pup weights and weight gains were decreased relative to the controls throughout lactation (decr 14-31%) in both sexes of the F1 generation. The greatest decreases in body weight gain were noted during PND 0-4 (before culling) (decr 28-31%), and the magnitude of decrease was reduced with time. Only sporadic, minor decreases were noted in the F1 generation after weaning, and these decreases were not considered adverse. Body weights and body weight gains in treated groups of the F2 generation were similar to the controls.

In both sexes of the F1 generation (except as noted), decreased terminal weight was observed at PND 4 and PND 21 (decr 14-21%). Decreased absolute brain weight (decr 11-15%) and absolute and relative (to body weight) thymus (decr 35-48%) and spleen (decr 19-44%) were noted at PND 4. Decreased absolute brain weight (decr 4% each sex), absolute and relative thymus in males (decr 16-29%), and absolute thymus weights in females (decr 24%) were observed at PND 21. At PND 21 in the males, decreased terminal body weight (decr 16%), absolute brain weight (decr 4%) and absolute and relative thymus weights (decr 16-29%) were noted.

In both sexes of the F2 generation, decreased absolute and relative (to body weight) thymus (decr 22-41%) and spleen (decr 25-34%) were noted at PND 4 and decreased absolute and relative thymus were also observed (decr 21-34%) at PND 21. Thymus weights were similar to controls by 10 weeks of age. Thus, the effect on body weight and organ weights were transient, suggesting a delay in development.

In the F1 offspring on PND 4, an increased incidence of dark green abnormal contents of the small intestine was observed in males (4/10 treated vs 0/12 controls) and females (4/13 treated vs 0/15 controls). In the F2 generation at 10 weeks, an increased incidence of renal pelvis

dilatation was noted in males (3/10 treated vs 1/10 controls).

The offspring LOAEL is 3 mg/kg/day, based on decreased survival, body weight, and body weight gains; increased incidence of blackish abdominal cavity and dark green abnormal intestinal content; and decreased thymus and spleen weights in the F1 and/or F2 generations. The offspring NOAEL is 0.75 mg/kg/day.

For immunotoxicity, no treatment-related effect was observed on the anti-SRBC antibody response (humoral immune response) or on the delayed-type hypersensitivity to KLH (cell-mediated immune response) in F1 or F2 males at 10 weeks of age. Significant decreases of thymus weights were observed at 3 mg/kg/day group in the F1 and F2 generations. No histopathology was performed. When thymus or spleen weights were decreased, there was usually a corresponding decrease in cellularity and a reduction in one or more lymphocyte subsets. However, only minor changes were noted in the proportions of lymphocyte subsets (on a percentage-basis). This effect resulted in a corresponding transient effect on thymus and/or spleen cellularity. In addition, the functional tests (humoral or cell-mediated immune response) did not demonstrate any compromise in rats at 10 weeks of age. Therefore, any effect on the cellularity and the changes of lymphocyte subsets is considered secondary to the effect on development and transient.

No significant treatment-related effects were noted on the immune system. The immunotoxicity LOAEL was not observed. The immunotoxicity NOAEL was 3 mg/kg/day, the highest dose tested.

This study is classified **acceptable/non-guideline; however, it can be used to satisfy guideline requirements for an immunotoxicity study (OPPTS 870.7800)** since it has provided adequate information for evaluation of immune function upon exposure to the test substance.

COMPLIANCE: Signed and dated Quality Assurance, Data Confidentiality, and Flagging statements were provided. A GLP Compliance statement was provided that stated the Submitter of this study was neither the Sponsor of this study nor conducted it and does not know whether it has been conducted in accordance with 40 CFR Part 160.

Reproduction and Fertility Effects-Rat; OPPTS 870.3800

EXECUTIVE SUMMARY: In a two-generation reproduction toxicity study (MRID 47447817), OMI-88 (tolfenpyrad; 99.33%; Lot # 6D-01-2) was administered in the diet to 30 Sprague Dawley (Crj:CD) rats/sex/dose group at dietary levels of 0, 0.75, 1.5, or 3.0 mg/kg/day for two successive generations with one litter per generation. The P generation animals were fed the test diets for ten weeks prior to mating to produce the F1 litters. The F1 litters were culled on post-natal day (PND) 4 to eight pups/litter (four/sex where possible). On PND 21, one male and one female pup from 24 litters in the 0, 0.75, and 1.5 mg/kg/day dose groups and 22 litters (all litters used) in the 3.0 mg/kg/day group were selected and fed the same test diet concentration as their dam. These animals were fed the test diets for ten weeks prior to mating (at 13 weeks of age) to produce the F2 litters.

No treatment-related effects were observed on organ weights, or macroscopic or microscopic findings.

At 3.0 mg/kg/day, two P females began parturition on GD 23. Both dams showed a decrease in locomotor activity, reddish tears, and prone position; one of these dams (# 50428) died on GD 24, and the other (# 50406) was killed and necropsied on GD 24 without completing parturition. A third dam (# 50421) exhibited signs of parturition on GD 23 including hemorrhage from the vagina, along with reddish nasal discharge, anemia, and finally death on GD 23. Additionally in the P females, one dam (# 50413) showed vaginal hemorrhage, reddish nasal discharge, anemia, and total litter loss on LD 0.

During the pre-mating period at 3.0 mg/kg/day, body weights were decreased in the P females, and in the F1 males and females. In the P females, cumulative body weight gains were decreased at all intervals beginning on PND 21 and continuing throughout pre-mating. Food consumption was decreased in the P and F1 males and females. Additionally at 3.0 mg/kg/day during the post-mating period, body weights, cumulative body weight gains, and food consumption were decreased in the P males, and body weights were decreased in the F1 males.

During gestation in the P generation, body weights were decreased in the 1.5 mg/kg/day dams on GD 7-20, and in the 3.0 mg/kg/day dams throughout gestation (GD 0-20), resulting in decreased cumulative gestational body weight gains. Food consumption was also decreased in the 3.0 mg/kg/day females throughout gestation. During gestation in the F1 generation, body weights were decreased in the 3.0 mg/kg/day dams, resulting in decreased cumulative gestational body weight gains. Food consumption was decreased on GD 14 and 20.

During lactation, body weights were decreased in the 1.5 mg/kg/day P dams on LD 0, and in the 3.0 mg/kg/day P dams on LD 0-7, and in the 3.0 mg/kg/day F1 dams on LD 0-4. Food consumption was decreased in the 3.0 mg/kg/day P females on LD 21, and in the 1.5 and 3.0 mg/kg/day F1 dams. However, cumulative lactational body weight gains were increased in the 3.0 mg/kg/day P and F1 dams, respectively, and food efficiency was generally increased in these doses in both generations, reflecting the recovery in body weight gains.

The LOAEL for parental toxicity is 3.0 mg/kg/day, based on decreased body weight and body weight gains, decreased motor activity, reddish tears, and prone position prior to death in two dams The NOAEL is 1.5 mg/kg/day.

No treatment-related effects were noted on the viability or lactation indices, sex ratio on PND 21, on the day of attainment of criterion for either balanopreputial separation or vaginal patency, organ weights, or on gross or microscopic pathological findings.

In the 3.0 mg/kg F1 offspring, decreases were observed in the mean total number of live pups on PND 0 and 4 (pre-culling), and mean number of female pups on PND 4 (post-culling) and 21. Additionally, the birth and live birth indices were lower at this dose compared to controls.

Decreased pup body weights were observed at 3.0 mg/kg in the F1 pups from PND 0-21 and in the F2 pups from PND 4 (pre-cull) through 21.

At 3.0 mg/kg, pinna unfolding was delayed in the F1 males and females on PND 2 and 3, and in the F2 males and females on PND 3. The day of eye opening was delayed in the F1 females and the F2 males. Surface righting reflex was delayed in the F1 males. All of these observations were considered to be related to the reduced body weights and body weight gains observed during lactation.

The LOAEL for offspring toxicity is 3.0 mg/kg, based on decreased pup viability and body weights, and delays in attainment of developmental landmarks. The NOAEL is 1.5 mg/kg.

No differences were observed in mean estrus cycle length in either generation. The number of primordial follicles, primary follicles, and total number of these follicles were similar between the control and 3.0 mg/kg/day groups in both generations. No treatment-related differences were observed in any of the measured sperm parameters in either generation. There were no effects of treatment on copulatory interval, or copulation or fertility indices in either generation.

In the 3.0 mg/kg/day P females, the gestation index was decreased, gestation duration was increased, four dams showed abnormal parturition, and four dams had total litter loss.

The LOAEL for reproductive toxicity was 3.0 mg/kg/day, based on decreased gestation index, increased gestation duration, abnormal parturition, and total litter loss. The NOAEL is 1.5 mg/kg/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

Oral Chronic Toxicity study -Dog; OPPTS 870.4100

EXECUTIVE SUMMARY: In a chronic oral toxicity study (MRID 47447818), OMI-88 technical (tolfenpyrad; 99.33% a.i.; Lot # 6D-01-2) was administered to four beagle dogs/sex/dose group daily by capsule at doses of 0, 1, 5 or 20 mg/kg/day for at least 12 months. However, the high dose was reduced to 10 mg/kg/day on Week 5 for the remainder of the study because of excessive toxicity.

No adverse, treatment-related effects were observed on ophthalmoscopic examinations, hematology, urinalysis, organ weights or gross pathology. At 5 mg/kg/day, vomiting was observed in both sexes at greater frequency primarily during the first four weeks of dosing, and one male had serum alanine aminotransferase increased at Months 9 and 12 by 755% and 138%, respectively. These findings were considered to be treatment-related, but in the absence of evidence of systemic toxicity, were not considered to be adverse.

Toxicity was observed in the 20/10 mg/kg/day group. Two premature deaths occurred. One male (#4004) died on Day 83. This dog presented with vomiting and abnormal feces (soft, watery, or mucus appearance, sometimes containing what appeared to be the test material) soon after the initiation of treatment. Beginning on Week 4, this dog displayed salivation, no defecation, decreased spontaneous movement, staggering gait, ananastasia, and hypothermia and was emaciated beginning on Week 6. At 1 to 2 weeks prior to death, this male also was observed with lateral position, abdominal respiration, oligopnea, and paleness of the conjunctival and oral mucosa. One female (#4103) died on Day 26. This animal was observed with vomiting and abnormal feces (soft and mucus appearance) during Weeks 1-4, and salivation, no defecation, and decreased spontaneous movement during Week 4. Additionally at this dose, vomiting was observed at greater frequency in the surviving dogs, particularly during the first four weeks of dosing. Soft feces were noted 1-4 times/week in the females during the first eleven weeks of dosing. Although these findings were observed during the first week, it could not be determined from the data as reported whether they were observed on Day 1. Treatment-related decreases in body weights, overall (Week 0-52) body weight gains, and food consumption were observed. The male that died generally lost body weight from Week 0 to time of death and had low food consumption (<200 g/day) from Week 3 on, with no food consumed during Weeks 5 and 6. Another male generally lost weight from Week 36 to Week 52, had low food consumption during Weeks 38, 41-45, 48, and 51, and it was noted that this dog's weight was lower than the lightest control, resulting in decreased group mean food consumption on Week 52. In the females, overall body weight gains were decreased by 33%. This was due to two dogs that had weight fluctuations throughout treatment and frequent periods of low food consumption, resulting in overall body weight gains that were lower than the lowest control and decreased ($p \leq 0.05$) group mean food consumption on Week 5. Additionally, the female that died generally lost weight from Week 0 (9.0 kg) to time of death (Week 3; 8.7 kg), and had low food consumption prior to death. Negative food efficiencies were frequently observed at 20/10 mg/kg/day, especially in the first 6-8 weeks, reflecting body weight losses in individual animals. Serum alanine aminotransferase (GPT) was increased in one 20/10 mg/kg/day male at Month 12 by 243% over controls. Treatment-related microscopic findings were observed in the liver. Mild to severe increased cytoplasmic eosinophilia of the hepatocytes was observed in 2/4 males and 3/4 females, both compared to 0/4 controls. Additionally in the females, the following findings were noted: (i) mild pigmentation in the hepatocytes in 2/4 dogs compared to slight in 1/4 controls; (ii) slight pigmentation in the Kupffer's cells in 2/4 dogs compared to 0/4 controls; (iii) mild to moderate pigment in the hepatocytes by Schmorl's stain in 2/4 dogs compared to slight in 3/4 controls; (iv) slight to mild pigment in the Kupffer's cells by Schmorl's stain in 2/4 dogs compared to slight in 2/4 controls; (v) mild pigment in the hepatocytes by Berlin blue stain in 2/4 dogs compared to slight in 3/4 controls; and (vi) slight to mild pigment in the Kupffer's cell by Berlin blue stain in 3/4 dogs compared to slight in 2/4 controls. **The LOAEL is 10 mg/kg/day, based on mortality, vomiting, decreased body weights, body weight gains, food consumption, increased serum alanine aminotransferase in the males, and microscopic liver findings in males and females. The NOAEL is 5 mg/kg/day.**

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4100b; OECD 452) for a chronic oral toxicity study in dogs.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided; however, the Submitter stated that they were neither the Sponsor nor Performing Laboratory of this study, and do not know if it was conducted in accordance with 40 CFR Part 160.

Combined Chronic Toxicity/Carcinogenicity Feeding – Rat; OPPTS 870.4300

EXECUTIVE SUMMARY: In a combined chronic toxicity/carcinogenicity study (MRID 47463704), 50 Fischer (F344/DuCrj) rats/sex/dose were exposed to OMI-88 (Tolfenpyrad; 99.33%; Lot No.: 6D-01-2) over 104 weeks in the diet at concentrations of 0, 15, 40, or 80 ppm (equivalent to 0/0, 0.561/0.686, 1.50/1.85, and 3.07/3.79 mg/kg/day in males/females). An additional 10 rats/sex/dose were treated similarly for 53 weeks and then sacrificed.

No test substance-related effects were observed on mortality, clinical signs, food efficiency, ophthalmoscopic examinations, hematology, clinical chemistry, urinalysis, or organ weights.

Systemically, the following statistically significant changes were noted in the 80 ppm group: decreased body weight, body weight gain, and food intake of males and females, increased incidences of white patched areas in the livers of females at Week 105, increased incidences of dark brown changes in the kidneys of males and females at Week 105, hypertrophy of the renal proximal tubular epithelial cells in males and females at Week 105, increased incidences of brown changes in Harderian glands of males and females at Week 105, increased hypersecretion of Harderian glands of males and females at Week 105, an increase in mast cells in the mesenteric lymph nodes of males at Week 105, increased sinus histiocytosis in the mesenteric lymph nodes of males and females at Week 105, and increased incidences and severity of foci of altered hepatocytes (basophilic) in females at Weeks 53 and 105. Hyaline droplets in the renal proximal tubular epithelial cells were observed more frequently in high dose males than controls at Week 53, but not at Week 105.

At 40 ppm, slight, but statistically significant reductions in body weight, body weight gains and food consumption were observed throughout treatment in females. Grossly, the incidence of brown change in the Harderian gland was elevated in males. Non-neoplastic histopathological changes included increased sinus histiocytosis in mesenteric lymph nodes, hypertrophy of the proximal tubular epithelial cells of the kidney and increased foci of altered hepatocytes (basophilic) in females at Week 105. Hyaline droplets in the renal proximal tubular epithelial cells of the kidney were observed more frequently in mid dose males than controls at Week 53, but not at Week 105.

The LOAEL is 40 ppm (equivalent to 1.50/1.85 mg/kg/day in males/females), based on decreased body weight, body weight gain, and food consumption of females, gross changes in the Harderian glands of males, and histopathological changes in the liver, kidney and mesenteric lymph nodes of females and the kidney of males. The NOAEL is 15 ppm (equivalent to 0.561/0.686 mg/kg/day in males/females).

At the doses tested, there was no treatment related increase in tumor incidence when compared

to controls. Dosing was considered adequate based on decreased body weights, body weight gains and food consumption, and gross and/or pathological findings in both sexes at 40 ppm.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4300; OECD 453) for a combined chronic toxicity/carcinogenicity study in rats.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided. The Submitter of the study stated that they were neither the Sponsor of the study nor conducted it, and did not know if it had been conducted in accordance with 40 CFR Part 160.

Carcinogenicity Study -Mouse; OPPTS 870.4200b

EXECUTIVE SUMMARY: In a carcinogenicity study (MRID 47463703), Tolfenpyrad (OMI-88; 99.33% a.i.; Lot No. 6D-01-2) was administered in the diet to CD1 mice (50/sex/dose) for up to 18 months at doses of 0, 15 or 150 ppm (equivalent to 0, 2.2/2.8, and 20.8/27.1 mg/kg bw/day in males/females). An additional group of 50 mice/sex/dose was treated similarly at a dose of 500 ppm for Weeks 1-12, 400 ppm for Weeks 13-19, and 300 ppm for Weeks 20-79 (60.9/75.9 mg/kg bw/day in males/females). The dose for the high group was adjusted twice due to observed toxicity.

No treatment-related effects were observed on hematology parameters or organ weights.

During the first 19 weeks there was an increased incidence of unscheduled deaths in the 400/500 ppm group (5 each treated vs 0 controls). After Week 19 when the high dose was lowered to 300 ppm, mortality was similar in all treated groups to the controls, or any effects were unrelated to dose. At 400/500 ppm (during Weeks 1-12), thinness was noted in both sexes, and some females were hypoactive and/or hunched (sometimes with distal tail sore/scab). These data suggest that 400 ppm or more may exceed the maximum tolerated dose.

At 300 ppm (during Weeks 20-79), the following findings were noted (# affected in treated group vs controls): ear sores/scabs in both sexes, ears missing in males, distal tail missing in both sexes, and distal tail sore/scab in females.

Decreased ($p<=0.05$) body weights compared to controls were observed in the 150 (decr 3-9%) and 300 ppm males (decr 9-28%) and the 300 ppm females (decr 11-24%). These decreases contributed to an overall (Weeks 1-78) body weight gain decrease in the 150 (decr 18%) and 300 ppm males (decr 49%) and the 300 ppm females (decr 47%). Body weight gain reductions ($p<=0.05$) were also noted in these groups for the intervals of Weeks 1-12 (decr 14-72%; treated at 500 ppm) and Weeks 13-20 (decr 80-100%; treated at 400 ppm), but body weight gains in these treated groups during Weeks 21-78 (treated at 300 ppm) were statistically similar to controls. Nevertheless, adverse effects on body weight and body weight gain were considered to be observed at 150 ppm and above, based on the overall body weight gain decrease of 18% at 150 ppm. Decreased ($p<=0.05$) overall (Weeks 1-78) food consumption compared to the controls was observed in both sexes at 150 (decr 8-9%) and 300 ppm (decr 14-16%). Generally,

decreases in food consumption were largest in magnitude during the first 12 weeks of treatment at 500 ppm. Decreased (not analyzed statistically) mean food efficiency was noted at 300 ppm in the males (decr 41%) and females (decr 24%).

Considering all animals (n=50) at 300 ppm, increased incidences of the gross observations sore ears in males (34% treated vs 18% controls) and females (28% vs 10%) and small uterus (14% vs 0%) were noted. Histologically, increased incidences of atrophy were observed at 300 ppm in the ovary, uterus, and cervix (28-38% treated vs 0% controls). The histological correlates for ear lesions observed clinically and grossly were ulcers and inflammation.

The LOAEL is 150 ppm (equivalent to 21/27 mg/kg bw/day in males/females), based on decreased body weights, body weight gains, food consumption in both sexes, and clinical signs (increased incidence of missing ears in males and ear sores and scabs in females). The NOAEL is 15 ppm (equivalent to 2.2/2.8 mg/kg/day in males/females).

At the doses tested, there was no treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreased body weights, body weight gains, food consumption, and food efficiency, and increased incidence of clinical signs, sore ears, and small uterus.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200b; OECD 451] in mice.

COMPLIANCE: Signed and dated GLP Compliance, Quality Assurance, Flagging, and Data Confidentiality statements were provided.

Bacterial Reverse Mutation Assay; OPPTS 870.5100

EXECUTIVE SUMMARY: In two independent trials of a reverse gene mutation assay in bacteria (MRID 47463705), *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 and *Escherichia coli* strain WP2*uvr*A were exposed to OMI-88 Technical (Tolfenpyrad; 99.33% a.i., Batch No. 6D-01-2) in dimethyl sulfoxide (DMSO) at concentrations of 0, 8, 40, 200, 1000, or 5000 µg/plate (all strains, +/-S9, Trial 1) and 0, 62.5, 125, 250, 500, or 1000 µg/plate (all strains, +/-S9, Trial 2). The S9 fraction was derived from the livers of male Sprague-Dawley rats induced with Aroclor 1254™. The standard plate incorporation method was used in Trial 1 (+/-S9) and Trial 2 (-S9), a pre-incubation step was added in Trial 2 (+S9). Standard strain-specific mutagens served as positive controls.

OMI-88 Technical was tested at up to the limit of solubility (+/-S9). Cytotoxicity (thinning of background lawn and/or reduction in numbers of revertants) was observed in several strains (TA1535, TA1537, and TA102) at 500 and/or 1000 µg/plate in the pre-incubation test (Trial 2, +S9). There were no treatment-related increases in the mean number of revertants/plate in any strain in either trial (+/-S9). The positive controls induced marked increases in revertant colonies compared to controls in all strains in the presence and absence of S9-activation. **There was no evidence of induced mutant colonies over background.**
The study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS

870.5100; OECD 471) for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided.

Bacterial Reverse Mutation Assay; OPPTS 870.5100

EXECUTIVE SUMMARY: In two independent trials of a reverse gene mutation assay in bacteria (MRID 47447822), *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2*uvr*A were exposed to OH-PT (metabolite of Tolfenpyrad, 99.9% a.i.; Lot No. Y980423) in dimethyl sulfoxide (DMSO) as follows: 0, 2.44, 4.88, 9.77, 19.5, 39.1, 78.1, 156, and 313 µg/plate (strains TA100, TA1535, and TA1537, -S9); 0, 9.77, 19.5, 39.1, 78.1, 156, 313, 625, and 1250 µg/plate (strains TA98 and WP2*uvr*A, -S9); 0, 9.77, 19.5, 39.1, 78.1, 156, 313, 625, and 1250 µg/plate (strains TA98, TA100, and WP2*uvr*A, +S9); 0, 39.1, 78.1, 156, 313, 625, 1250, 2500, and 5000 µg/plate (strain TA1535, +S9); and 0, 2.44, 4.88, 9.77, 19.5, 39.1, 78.1, 156, and 313 µg/plate (strain TA1537, +S9). The S9 fraction was derived from the livers of male Sprague-Dawley rats induced with phenobarbital and 5,6-benzoflavone. The standard plate incorporation method with a pre-incubation step was used both with and without S9-activation. Standard strain-specific mutagens served as positive controls.

OH-PT was tested at up to the limit of solubility (+/-S9). With the exception of strain TA98, cytotoxicity (thinning of background lawn) was observed in all strains ≥625 –S9 and ≥2500 µg/plate +S9. There were no treatment-related increases in the mean number of revertants/plate in any strain with or without S9. The positive controls induced marked increases in revertant colonies compared to controls in all strains in the presence and absence of S9-activation. **There was no evidence of induced mutant colonies over background.**

The study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.5100; OECD 471) for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided. However, an additional GLP compliance statement was provided which stated that the submitter of the study was neither the Sponsor nor conducted the study, and does not know if the study was conducted in accordance with 40 CFR Part 160.

***In Vitro* Mammalian Cell Gene Mutation Test; 870.5300, OECD 476**

EXECUTIVE SUMMARY:

***In Vitro* Mammalian Chromosome Aberration Test; OPPTS 870.5375**

EXECUTIVE SUMMARY: In a mammalian cell cytogenetics assay (chromosome aberration; MRID 47447824), Chinese hamster lung (CHL) cell cultures were exposed to OMI-88 (Tolfenpyrad; 99.33% a.i.; Batch # 6D-01-2) in DMSO at concentrations of 0, 4.9, 7.1, 10.1, 14.4, 20.6, 29.4, 42.0, 60.0, 85.8, 123, 175, or 250 µg/mL for either 6 hours with an 18 hour

recovery period in the presence of S9 or for 24 hours of continuous treatment in the absence of S9. In Trial 2, cell cultures were exposed at the following concentrations: 0, 32.8, 41.0, 51.2, 64.0, 80.0, or 100 µg/mL for 6 hours with an 18 hour recovery period in the presence of S9; 0, 8.6, 10.7, 13.4, 16.8, 21.0, 26.2, 32.8, 41.0, or 51.2 µg/mL for either 24 or 48 hours of continuous exposure in the absence of S9; and 0, 21.0, 26.2, 32.8, 41.0, 51.2, 64.0, 80.0, and 100 µg/mL for 6 hours with an 18 hour recovery period in the absence of S9. The S9 fraction was derived from the livers of male Sprague-Dawley rats induced with Aroclor™ 1254. Cyclophosphamide and methylmethanesulfonate served as positive controls in the presence and absence of S9, respectively.

OMI-88 was tested up to cytotoxic concentrations (i.e., levels that induced a ≥50% decrease in cell numbers) both in the presence and absence of S9. In both independent trials, no significant increases in the percentage of cells with structural aberrations (excluding gaps) were observed at any concentration at any exposure interval in the presence or absence of S9. It was noted that cultures treated with OMI-88 for 24 and 48 hours in the absence of S9 in Trial 2 resulted in a marked increase in the frequency of cells with numerical chromosome aberrations (predominantly polyploidy) that exceeded the historical control range. However, this effect decreased with an increase in dose. Similarly, a significant effect was only observed at the low-dose (10.1 µg/mL) during Trial 1 (24 hr, -S9). The biological significance of polyploidy *in vitro* is not completely understood at the present time. Therefore, this finding was not considered to be an adverse treatment-related effect. The positive controls induced the appropriate response in the presence and absence of S9 in both trials. **There was no evidence of structural chromosome aberrations induced over background in the presence or absence of S9-activation.**

This study is classified as **acceptable/guideline** and satisfies the Guideline requirement (OPPTS 870.5375, OECD 473) for *in vitro* mutagenicity (chromosome aberration) data.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided.

***In Vitro* Mammalian Chromosome Aberration Test; OPPTS 870.5375**

EXECUTIVE SUMMARY: In a mammalian cell cytogenetics assay (chromosome aberration; MRID 47447826), Chinese hamster lung (CHL/IU) cell cultures were exposed to OH-PT (metabolite of Tolfenpyrad, 99.9% a.i.; Lot No. Y980423) in dimethyl sulfoxide (DMSO) at concentrations of 0, 40, 80, 120, 160, or 200 µg/mL for 6 hours with an 18 hour recovery period both in the presence and absence of S9, or at 0, 10, 30, 50, 70, 90, 110, or 130 µg/mL for 24 or 48 hours of continuous treatment in the absence of S9. The S9 fraction was derived from the livers of male Sprague-Dawley rats induced with phenobarbital and 5,6-benzoflavone. Cyclophosphamide and mitomycin C served as positive controls in the presence and absence of S9, respectively.

OH-PT was tested up to cytotoxic concentrations (+/-S9). Based on the cytotoxicity observed, the following concentrations were selected for evaluation: 40, 80, 120, and 160 µg/mL (6 hrs,

+S9); 40, 80, and 120 µg/mL (6 hrs, -S9); 10, 30, 50, 70, and 90 µg/mL (24 hrs, -S9); and 10, 30, 50, and 70 µg/mL (48 hrs, -S9). No positive results [incidence of cells with structural aberrations (excluding gaps) >=10%] or dose-dependent increases in the percentage of cells with structural aberrations (excluding gaps) were observed at any concentration after exposure for 6 hours (±S9), 24 hours (-S9), or 48 hrs (-S9). Additionally, the incidence of polyploidy was similar to controls at all doses under all conditions. The positive controls induced the appropriate response in the presence and absence of S9. **There was no evidence of structural chromosome aberrations induced over background in the presence or absence of S9-activation.**

This study is classified as **acceptable/guideline** and satisfies the Guideline requirement (OPPTS 870.5375, OECD 473) for *in vitro* mutagenicity (chromosome aberration) data.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided. However, the GLP Compliance statement stated that the submitter of this study was neither the sponsor of the study nor conducted it, and does not know if it was conducted in accordance with 40 CFR Part 160.

Mammalian Bone Marrow Chromosome Aberration Test; OPPTS 870.5385

EXECUTIVE SUMMARY:

Micronucleus Assay in Rats; OPPTS 870.5395

EXECUTIVE SUMMARY: In a bone marrow micronucleus assay (MRID 47447827), 6 or 10 male Crj:CD(SD)IGS rats dose were treated twice (24 hrs apart) via gavage (10 mL/kg) with OH-PT (metabolite of Tolfenpyrad; 99.9% a.i., Lot No. Y000328) in 0.5% carboxymethyl-cellulose at doses of 0, 5, 10, or 20 mg/kg. Bone marrow cells were harvested at 24 hours after the final dosing. Cyclophosphamide (20 mg/kg) administered once via gavage served as the positive control.

At 20 mg/kg, one rat was found dead during the observation period (no further details were provided). Significant decreases ($p<0.05$) in incidence of PCEs (%) were observed in all treatment groups (decr 10-22%) compared to controls, indicating that the test material inhibited the growth of bone marrow cells. No treatment-related increases in the MPCE frequency were observed in any treatment group when compared to controls. The positive control induced the appropriate response. **There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any treatment time.**

However, the study is not complete because female rats were not tested and no justification was provided to waive the requirement for both sexes.

This study is classified as **unacceptable/guideline** and does not satisfy the guideline requirement (OPPTS 870.5395; OECD 474) for *in vivo* cytogenetic mutagenicity data. Nevertheless, the study can be upgraded if a rationale for testing only males can be provided.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided. However, the GLP Compliance statement stated that the submitter of this study was neither the sponsor of the study nor conducted it, and does not know if it was conducted in accordance with 40 CFR Part 160.

Acute Neurotoxicity Study; OPPTS 870.6200

EXECUTIVE SUMMARY: In an acute neurotoxicity study (MRID 47447831), OMI-88 (Tolfenpyrad; 99.5% a.i.; Lot # 365-65A) in corn oil was administered once via gavage (5 mL/kg) to 10 Sprague-Dawley rats/group at dose levels of 0, 20, 40, or 60 mg/kg in males and 0, 10, 20, or 40 mg/kg in females, and the animals were observed for up to 14 days post-dosing. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed on 10 rats/sex/group at pre-dosing and Days 1 (approximately 6 hours post-dosing; estimated time of peak effect), 8, and 15. At study termination, 5 rats/sex/group were anesthetized and perfused *in situ* for neuropathological examination. The tissues from the perfused animals in the control and high-dose (60 mg/kg males and 40 mg/kg females) groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues. Acceptable positive control data were provided.

No compound-related effects were observed in FOB parameters, motor activity, brain weights, or gross or neuropathology in either sex.

In the 40 mg/kg males, transient decreases (decr 8-9%) in body weight were noted at Days 2-4, and body weight gains were decreased by 30% during Week 1. Despite increases (not statistically significant, NS) in body weight gain (incr 11%) during Week 2, overall (Days 1-15) body weight gains remained decreased by 9% at this dose. On Days 1-2, decreases were observed in both absolute (decr 76%) and relative (decr 75%) food consumption. The Sponsor stated that due to an error, only 5 of the 10 feed values for the males were recorded on Day 1 and none of the feed values were recorded on Day 2. Therefore, food consumption during the first few days of the study cannot be definitively evaluated for the males. However, because similar decreases in food consumption were observed in the treated females during Days 1-2, the reviewers considered these findings in the males to be indicative of a treatment-related effect.

In the 60 mg/kg males, the following treatment-related clinical signs (# affected/10 treated vs. 0/10 controls; unless otherwise stated) were observed: mild to severe dehydration (9 treated vs. 1 control); scant feces (6); soft or liquid feces (3); and chromorhinorrhea (3). Body weights were decreased throughout the post-dosing period compared to controls, and were significantly decreased by 7-16% on Days 2-12. Body weight gains were decreased by 76% during Week 1, and despite increases (NS) in body weight gain (incr 33%) during Week 2, overall body weight gains remained decreased by 19% at this dose. On Days 1-2, decreases were observed in both absolute (decr 85%) and relative (decr 84%) food consumption.

Effects in the 20 mg/kg males were limited to a minor transient decrease (decr 6%) in body weight on Day 2, and decreases in absolute (decr 64%) and relative (decr 63%) food

consumption on Days 1-2. However, body weight gain and both absolute and relative food consumption values for Weeks 1 and 2, and the overall study were similar to controls.

The systemic LOAEL in males was 40 mg/kg, based on decreased body weight, body weight gain, and absolute and relative food consumption. The systemic NOAEL in males is 20 mg/kg.

In the 10 mg/kg females, body weight gain was decreased by 46% during Week 1 and by 30% during the overall (Days 1-15) study. Absolute and relative food consumption were both decreased by 30% on Days 1-2.

In the 20 mg/kg females, transient decreases (decr 6-12% in body weight were noted at Days 2-7. Body weight gains were decreased by 61% during Week 1. Despite an increase (NS) in body weight gain (incr 17%) during Week 2, overall body weight gain remained decreased by 26% in this group. Decreases were noted in both absolute (decr 44%) and relative (decr 41%) food consumption on Days 1-2. During Week 2, absolute and relative food consumption were similar to or increased compared to controls. Overall absolute and relative food consumption were similar to controls.

At 40 mg/kg, one female rat (#27409) was found dead on Day 4. The following treatment-related clinical signs (# affected/10 treated vs. 0/10 controls) were observed: mild to severe dehydration (8) and urine-stained abdominal fur (7). Body weights were decreased throughout the post-dosing period compared to controls, and were significantly decreased by 8-21% on Days 2-13. During Week 1, body weight gains were decreased by 136%, as this group actually lost weight (-7.9 g treated vs. 21.7 g controls). Despite an increase in body weight gain (incr 90%) during Week 2, overall body weight gain remained decreased by 35% in this group. Decreases were noted in both absolute (decr 63%) and relative (decr 62%) food consumption on Days 1-2. Although absolute food consumption was similar to controls, and relative food consumption was increased by 18% during Week 2, decreases in overall absolute (decr 23%) and relative (decr 13%) food consumption were observed at this dose.

The systemic LOAEL in females was 20 mg/kg/day, based on decreases in body weight, body weight gain and absolute and relative food consumption. The systemic NOAEL in females was 10 mg/kg/day.

The FOB findings (decreases in body weight in the 60 mg/kg males and the 40 mg/kg females on Day 8, and the increased appearance score of the 40 mg/kg females on Day 1) were considered systemic effects. Motor activity was similar to controls, and no compound-related neurological lesions were observed at any dose in either sex. **Therefore, no neurological effects were observed at any dose in either sex.**

The neurotoxicity LOAEL was not observed. The neurotoxicity NOAEL is 60 mg/kg in males and 40 mg/kg in females.

The study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS

870.6200a) for an acute neurotoxicity study in rats.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

Subchronic Neurotoxicity Study; OPPTS 870.6200

EXECUTIVE SUMMARY: In a subchronic neurotoxicity study (MRID 47447830), OMI-88 (Tolfenpyrad, 99.33% a.i., Batch No. 6D-01-2) was administered in the diet to 10 Sprague-Dawley rats/sex/group at dose levels of 0, 15, 40, or 80 ppm (equivalent to 0/0, 1.0/1.2, 2.7/3.2, and 5.4/6.0 mg/kg/day [M/F], respectively) for 13 weeks. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed using all rats at pre-dosing and Weeks 2, 4, 8, and 12. At study termination, 5 rats/sex/group were anesthetized and perfused *in situ* for neuropathological examination. The tissues from the perfused animals in the control and 80 ppm groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues. Positive control data were not provided.

No compound-related effects were observed in mortality, clinical signs of toxicity, FOB, motor activity, ophthalmoscopic parameters, gross pathology, brain measurements, or neuropathology.

At 80 ppm, body weights (no statistical analyses reported) were decreased throughout the study in the males (decr <=5%) and in the females (decr 5-15%). Body weight gains were decreased ($p<0.05$) by 13% in the males during Weeks 0-8, and by 28 and 32% in the females during Weeks 0-8 and 8-13, respectively. Overall (Weeks 0-13) body weight gains were decreased by 8% in the males (NS) and by 29% ($p<0.01$) in the females. In the females, food consumption was decreased ($p<0.01$) by 17 and 18% during Weeks 1-8 and 9-13, respectively, and by 18% overall (Weeks 1-13), and food efficiency was decreased (no statistical analyses reported) by 14 and 22% during Weeks 1-8 and 9-13, respectively, and by 15% overall (Weeks 1-13).

No compound-related effects were observed at 15 or 40 mg/kg in either sex.

The systemic LOAEL was 80 ppm (equivalent to 5.4/6.0 mg/kg/day, M/F) based on decreased body weights, body weight gains, and food consumption. The systemic NOAEL is 40 ppm (equivalent to 2.7/3.2 mg/kg/day, M/F).

No neurological effects were observed at any dose in either sex.

The neurotoxicity LOAEL was not observed. The neurotoxicity NOAEL is 80 ppm (equivalent to 5.4/6.0 mg/kg/day, M/F).

The study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.6200b) for a subchronic neurotoxicity study in rats.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and

Quality Assurance statements were provided.

Cell Cycle Kinetics Assay in CHL Cells; Non-guideline

EXECUTIVE SUMMARY: In a cell cycle kinetics assay (MRID 47463707), Chinese hamster lung (CHL) cell cultures were exposed to Tolfenpyrad (99.5% a.i.; Lot # 365-65A) in dimethyl sulfoxide (DMSO) at concentrations of 0, 5, 7, 8.5, 10, 13, or 15 µg/mL for approximately 3, 6, or 24 hours in the absence of S9-activation. The cultures were harvested at 24 hours after initiation of treatment. The purpose of this study was to explain the polyploidy observed in a previously conducted Chinese hamster lung chromosome aberration study (MRID 47447824; reviewed concurrently).

Severe cell cycle delay was observed at the concentrations analyzed (5, 8.5, and 13 µg/mL) at all exposure times (3, 6, and 24 hours). The percentage of cells that completed 2 cell cycles was reduced at all concentrations as follows: after 3 hours of treatment (6.5-20.0% treated vs. 80.5% controls); after 6 hours of treatment (14.0-33.0% treated vs. 81.5% controls); and after 24 hours of treatment (4.0-32.0% treated vs. 66.5% controls). Treatment time was not a factor in cell cycle delay. Three hours of exposure was sufficient to arrest the cell cycle with little difference noted between the treatment times. Increases in polyploidy compared to controls were observed after 6 and 24 hours of treatment. The reviewers agree with the Sponsor that, in the absence of S9-activation, Tolfenpyrad causes cell cycle delay after exposure for as little as 3 hours and polyploidy after as little as 6 hours exposure. The polyploidy observed in the previous chromosome aberration study (MRID 47447824; reviewed concurrently) was likely due to the inhibition of cell cycle progression.

This study is classified as **acceptable/non-guideline** and provides data that supports cell cycle delay as an explanation for the polyploidy observed during *in vitro* testing.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

Metabolism Study-Rat; OPPTS 870.7485

EXECUTIVE SUMMARY: : In a series of metabolism studies in the rat (MRIDs 47447837, 47447836, and 47447834), [Pyrazole-3-^{14}C]-OMI-88 or [Tolyl-U-^{14}C]-OMI-88 (tolfenpyrad; Lot Nos. CFQ9339A, CFQ9339B, CFQ9338A, and CFQ9338B; radiochemical purity 98.4-99.7%) was administered to groups of F344 rats. Mass balance studies were conducted on five rats/sex with the following dose groups: in MRID 47447837, (i) a single 1 mg/kg oral gavage dose of [PY-^{14}C]-OMI-88 or [TO-^{14}C]-OMI-88 and (ii) a single 20 mg/kg oral gavage dose of [PY-^{14}C]-OMI-88; or in MRID 47447836, (iii) 14 daily 1 mg/kg oral gavage doses of [PY-^{14}C]-OMI-88 (males and females) or [TO-^{14}C]-OMI-88 (males only). Blood pharmacokinetic studies were conducted on five rats/sex given single 1 or 20 mg/kg oral gavage doses of [PY-^{14}C]-OMI-88 or [TO-^{14}C]-OMI-88, or 14 daily 1 mg/kg oral gavage doses of [PY-^{14}C]-OMI-88 (males and females) or [TO-^{14}C]-OMI-88 (males only). Tissue distribution and depletion studies were performed on fifteen rats/sex/dose group given: (i) a single 1 mg/kg oral gavage dose of [PY-

^{14}C]-OMI-88 or [TO-^{14}C]-OMI-88; (ii) a single 20 mg/kg oral gavage dose of [PY-^{14}C]-OMI-88; or (iii) 14 daily 1 mg/kg oral gavage doses of [PY-^{14}C]-OMI-88 (males and females) or [TO-^{14}C]-OMI-88 (males only). Five rats/sex/group were killed at 4 or 12 h for the 1 mg/kg groups, 6 or 24 h for the 20 mg/kg groups, or 168 h for all groups. Biliary excretion studies were conducted on four rats/sex following a single 1 or 20 mg/kg oral gavage dose of [PY-^{14}C]-OMI-88. The concentration time-courses of radioactivity in blood and plasma were plotted, the concentration and recovery of radioactivity in tissues and excreta were determined. Metabolites were identified and quantified in the urine, feces and bile (MRID 47447834). Study design and metabolite identification was based on the results of a preliminary mass balance study (MRID 47447833) and fate study (MRID 47447835).

There were no differences observed in the blood pharmacokinetic parameters between the [PY-^{14}C]- and [TO-^{14}C]-label positions in the single or multiple dose studies. Absorption of the test compound was rapid, with radioactivity detected in the blood 0.5 h after administration in the single dose study. In animals given a 1 mg/kg dose of [^{14}C]-OMI-88, blood levels of radioactivity reached mean maximum concentrations at 2-6 h post-dosing. A biphasic elimination was observed. In animals given a 20 mg/kg dose of [^{14}C]-OMI-88, blood levels of radioactivity reached a mean maximum concentration at 4-12 post-dosing. Biphasic elimination was not observed, suggesting a difference in the blood concentration-time profiles between the two doses. However, it was stated that a non-compartment model was used to calculate the elimination phase half-lives, due to poor data fit with the compartment model. The area under the concentration-time curves ($AUC_{0\rightarrow\infty}$) generally increased proportionally with dose. In the multiple dose study, the blood concentrations of radioactivity tended to plateau after the third administration, suggesting there was no bioaccumulation following repeated administration. In animals given multiple doses of [PY-^{14}C]-OMI-88, blood levels of radioactivity were approximately 2- to 3-fold higher in females than in males, reaching mean maximum concentrations at 12 h post-dosing in the females. Males receiving multiple doses of [TO-^{14}C]-OMI-88 had a maximum blood concentration at 8 h post-dosing, and biphasic elimination was observed.

Total recoveries ranged from 91.3-99.6% of the administered dose (AD) across all groups and in both sexes. The test compound was rapidly excreted. In the 1 mg/kg single dose groups, approximately 57.1-66.8% AD was eliminated during the first 24 h post-dosing, increasing to 83.8-85.1% AD at 48 h. In the 20 mg/kg single dose groups, excretion was somewhat slower, with 26.1-30.3% AD eliminated during the first 24 h post-dosing, increasing to 55.2-70.3% AD at 48 h. Feces were the predominant route of excretion. Across all single dose groups, 88.2-93.2% AD was excreted in the feces, and 1.7-3.0% AD was eliminated in the urine. There were no differences between the sexes at either dose. Negligible amounts of radioactivity were recovered in the expired air and cage wash, both accounting for ≤0.1% AD. Administration of repeated daily doses had no effect on the route of excretion or the extent of recovery. Excretion approached steady-state by the fourth administration of the test compound. In the bile duct-cannulated rats at 48 h post-dosing, the majority of radioactivity was excreted in the bile (51.3-69.5% AD), with minor amounts eliminated in the feces (3.5-8.3% AD) and urine (0.7-3.0% AD), indicating that bile was the primary route of excretion for the absorbed test material. Absorption (defined as radioactivity found in the bile, urine, cage wash, and carcass) was greater

in males (72.8-77.8% AD) than in females (57.9-69.4% AD). Females also had more radioactivity remaining in the gastrointestinal tract, and the amount remaining increased with dose.

The test compound did not distribute into the red blood cells; concentrations of radioactivity in plasma were never lower than those in whole blood in all groups. Generally, the highest concentrations of radioactivity were observed in the liver, kidney, brown fat and heart; a redistribution that also included white fat, bone marrow and skin was noted over time. Brown fat radioactivity concentrations were higher in females than in males. Radioactivity concentrations dropped substantially from 12 to 168 h post-dosing.

Tolfenpyrad was metabolized by oxidation (Pt-CA, OH-PT and OH-PT-CA), followed by conjugation (glucuronide, sulfate, asparagines or taurine). The primary metabolite, 4-[4-[(4-chloro-3-ethyl-1-methylpyrazol-5-yl)carbonylaminomethyl] phenoxy]benzoic acid (PT-CA), was present in the feces at 9.0-36.2% AD. PT-CA was also found in plasma, liver, kidney, and fat (<5%), and along with taurine-conjugated and hydroxylated forms, was also found in the bile at 4.6-22.3%, and in the feces and urine of bile duct-cannulated rats. Parent was identified in the feces at 0.3-14.8%, and the amount decreased with time (4.1-14.8% at 0-24 h vs. 0.3-3.0% at 24-48 h). The other identified fecal metabolites present at >5%AD were 4-[4-[(4-chloro-1-methyl-3-(1-sulfoxyethyl)pyrazol-5-yl) carbonylaminomethyl]phenoxy]benzoic acid (Sul-OH-PT-CA) and 4-[4-[(4-chloro-3-(1-hydroxyethyl)-1-methylpyrazol-5-yl)carbonylaminomethyl]phenoxy]benzoic acid (OH-PT-CA). In bile duct-cannulated rats, parent was found in small amounts in bile (0.1-0.4%) compared to feces (2.4-6.4%), suggesting that the parent indentified in feces was passing through the gastrointestinal tract unabsorbed. As bile was removed from the gastrointestinal tract of the bile duct-cannulated rats, it was considered that the PT-CA in the feces of these animals was formed by the action of enterobacteria in the gut. Parent was not found in the urine, plasma, liver, kidney or fat, particularly at t_{max}, indicating that parent was rapidly metabolized in the liver. A total of nine urinary metabolites were isolated and six were identified; however, none were present at >0.9% AD. Urinary metabolites were a mixture of cleavage products of the C-N bond of the benzylamine moiety, oxidation on the side chains of both radiolabeled rings, and conjugates, suggesting a complex metabolic profile.

These metabolism studies are collectively classified **acceptable/guideline** and when reviewed together satisfy the guideline requirement for a Tier 1 metabolism study [OPPTS 870.7485, OECD 417] in rats.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided. The Submitter of the study stated that they were neither the Sponsor of the study nor conducted it, and did not know if it had been conducted in accordance with 40 CFR Part 160. However, except for MRID 47447833, the study reports contained a statement from the Kashima Laboratory manager that the study was conducted according to US EPA 1989 GLP standards under FIFRA.

Dermal Penetration Study-Rat; OPPTS 870.7600

EXECUTIVE SUMMARY: In a dermal penetration study (MRID 47447839), [Pyrazole-^{14}C] Tolfenpyrad (≥92.6% radiochemical purity; Batch No. 1 [Code CFQ14881]) was applied to the shaved skin (10.5 cm^2) of Sprague Dawley rats. Actual doses of 0.91, 8.41, or 99.90 µg/cm^2 skin (0.1, 1, or 10 g/L formulations, respectively) were applied to the skin of each rat in volumes of 10 µl/cm^2 skin. Four males/dose/time point were tested using exposure durations and termination times of 0.5, 1, 2, 4, 10, or 24 hours post-administration.

Analytical recoveries were 89.0-95.6% AD. Very little of the applied dose was actually absorbed at any concentration (6.32-12.9% AD) at 24 hours post-dosing. The absorbable dose was 31.6-33.5% in the 0.1 and 1 g/L groups and 13.6% in the 10 g/L group. Most of the dose was not absorbed (47.8-51.0% in the 0.1 and 1 g/L groups and 71.8% in the 10 g/L group. The greatest amount absorbed (12.9%) and either absorbed or absorbable (44.5%) was noted in the 1 g/L group. The amount found in the skin was similar from 0.5-24 hours post-dose at 0.1 and 1 g/L (24.2-33.5% AD) and at 10 g/L (8.36-17.1% AD). Absorption continued throughout the 24 hour post-dosing period. In each group, the majority of the dose was isolated in the skin wash (sponges) and spreader (not absorbed), and substantial amounts were also isolated in the treated skin (absorbable dose).

Maximum counts per gram were observed as follows: (i) at 0.1 g/L: liver (2930 dpm/g at 24 hours), kidney (3049 dpm/g at 24 hours), and adrenals (2904 dpm/g at 2 hours); (ii) at 1 g/L: heart (35,024 dpm/g at 10 hours), liver (42,371 dpm/g at 24 hours), kidney (29,915 dpm/g at 10 hours), and fat at 24 hours (20,031 dpm/g); and (iii) at 10 g/L, fat (24,119 dpm/g at 24 hours), heart (19,613 dpm/g at 24 hours), kidney (12,566 dpm/g at 24 hours), and liver (22,806 dpm/g at 24 hours). Concentrations were 2177 dpm/g in the adrenals as soon as 0.5 hours post-dose in the 0.1 g/L group. Excretion of the absorbed dose via the urine was noted at all time points, but minimal amounts were found in the feces until 24 hours post-dose.

Given the uncertainty regarding deposition under actual field conditions, it is considered appropriate to derive an estimate of dermal absorption based on the results from the mid-dose group (1 g/L; actual dose 8.4 µg/cm^2 skin), as percent dermal absorption was greatest at this dose level. Based on the likely worker exposure time frame, it is considered most appropriate to adopt the dermal absorption value calculated for the group of animals for which the skin site was washed after 10 hours. Because absorption continued to occur throughout the study, the absorbable dose should also be considered in a conservative estimate of absorption. At 10 hours in the 1 g/L group, the absorbable and absorbed dose accounted for 36.5% of the applied dose.

Consistent with the tier approach to risk assessment, if a more refined estimate of dermal absorption is necessary to obtain adequate margins of exposure, further analysis of the toxicokinetics may yield a more appropriate value to use in the occupational risk assessment (e.g., maximum body loads at each dose).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.7600; OECD none) for a dermal penetration study in rats.

COMPLIANCE: Signed and dated GLP Compliance, Quality Assurance, and Data Confidentiality statements were provided.

In Vitro Metabolism; Non-guideline

EXECUTIVE SUMMARY: This study was performed to characterize oxidative metabolites in the initial phase of metabolism that are supposed to be intermediary metabolites *in vivo* in mammals and to extrapolate obtained results to main metabolic reactions in plants. OMI-88 (Tolfenpyrad) in ethanol was incubated with S9 for 3 hours. The incubation was terminated by extraction with acetonitrile. Extracts of incubations with unlabeled OMI-88 (0.1 mg/mL; 99.8% a.i.; Lot no. 6D-01-1) were analyzed to determine the molecular weights (by LC-MS) and structures of the HPLC-isolated metabolites through GC-MS, LC-MS/MS, and ^{1}H-NMR. Extracts of incubations with [Tolyl ring-U-^{14}C] OMI-88 (0.01 mg/mL; 98.8% radiochemical purity; Lot no. CFQ 9338) or [Pyrazole-3-^{14}C] OMI-88 (0.01 or 0.1 mg/mL; 99.3% radiochemical purity; Lot no. CFQ 9339) were analyzed by HPLC to quantify the metabolites present. Quantifying the metabolites from these incubations allowed the comparison of metabolism based on two different radiolabel positions in the test compound and two different quantities of test compound incubated with S9. Additionally, the metabolic profiles would determine if cleavage between the bonds of the pyrazole and tolyl rings occurs during the metabolism of the test compound.

Total recovery was 91.0-108.1% of the radioactivity added to the incubations, of which the parent compound accounted for 10.2-12.4%. Only 1.4-1.9% of the radioactive residues were found in unidentified compounds; the remaining approximately 88% of the isolated metabolites were identified. In addition to the parent, a total of 17 metabolites were identified. The primary metabolite was OH-PT-CA (24.5-32.4%); other major metabolites included PT-CA (13.4-16.2%), CO-PT-CA (9.3-13.2%), OH-PT (7.6-8.4%), PT-OH (6.7-7.7%), and OH-PT-OH (3.8-5.3%). The other metabolites were present at <5% of the total incubation dose.

The metabolic profiles were generally similar both qualitatively and quantitatively, regardless of the radiolabel position or the amount of radiolabled compound added (0.1 or 1.0 mg) to the incubation with S9. The only exceptions were that OH-PAM and CO-PAM were minor metabolites exclusive to incubations with [PY-^{14}C] OMI-88, while OH-T-CA and CA-T-CA were minor metabolites exclusive to incubations with [TO-^{14}C] OMI-88. These metabolites indicate that cleavage of the bonds between the pyrazole and tolyl rings can occur, but that this is only a minor metabolic pathway (5-6%).

The main metabolic pathways included the oxidations of the methyl moiety of T-CH_3 and ω-1 carbon of CH_3CH_2-P. The oxidation of these two carbons resulted in the formation of the hydroxylated metabolites PT-OH, OH-PT, and OH-PT-OH. Further oxidation leads to the metabolites PT-CHO, PT-CA, OH-PT-CA, CO-PT, CO-PT-OH, and CO-PT-CA. Other metabolic pathways include the bond cleavage of the amide and methylene moieties, the demethylation of N-CH_3, or the formation of the vinyl group after hydroxylation of CH_3CH_2-P.

This *in vitro* study is classified **acceptable/non-guideline** and determined the metabolites of

Tolfenpyrad radiolabeled in two different positions and incubated with S9 at two different quantities. Although the stated purpose was to also extrapolate these results to the main metabolic reactions in plants, no information was provided in this study to allow such extrapolation.

COMPLIANCE: A signed and dated Data Confidentiality statements was provided. A signed and dated GLP Compliance was provided that states the submitter of this study does not know whether it was conducted in accordance with 40 CFR Part 160. A Quality Assurance statement was not provided.